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Operational response to malaria epidemics: are rapid diagnostic tests cost-effective?

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Summary

OBJECTIVE To compare the cost-effectiveness of malaria treatment based on presumptive diagnosis with that of malaria treatment based on rapid diagnostic tests (RDTs).

METHODS We calculated direct costs (based on experience from Ethiopia and southern Sudan) and effectiveness (in terms of reduced over-treatment) of a free, decentralised treatment programme using artesunate plus amodiaquine (AS + AQ) or artemether-lumefantrine (ART-LUM) in a *Plasmodium falciparum* epidemic. Our main cost-effectiveness measure was the incremental cost per false positive treatment averted by RDTs.

RESULTS As malaria prevalence increases, the difference in cost between presumptive and RDT-based treatment rises. The threshold prevalence above which the RDT-based strategy becomes more expensive is 21% in the AS + AQ scenario and 55% in the ART-LUM scenario, but these thresholds increase to 58 and 70%, respectively, if the financing body tolerates an incremental cost of 1 € per false positive averted. However, even at a high (90%) prevalence of malaria consistent with an epidemic peak, an RDT-based strategy would only cost moderately more than the presumptive strategy: +29.9% in the AS + AQ scenario and +19.4% in the ART-LUM scenario. The treatment comparison is insensitive to the age and pregnancy distribution of febrile cases, but is strongly affected by variation in non-biomedical costs. If their unit price were halved, RDTs would be more cost-effective at a malaria prevalence up to 45% in case of AS + AQ treatment and at a prevalence up to 68% in case of ART-LUM treatment.

CONCLUSION In most epidemic prevalence scenarios, RDTs would considerably reduce over-treatment for only a moderate increase in costs over presumptive diagnosis. A substantial decrease in RDT unit price would greatly increase their cost-effectiveness, and should thus be advocated. A tolerated incremental cost of 1 € is probably justified given overall public health and financial benefits. The RDTs should be considered for malaria epidemics if logistics and human resources allow.

keywords *Plasmodium falciparum*, malaria, epidemic, rapid diagnostic test, presumptive treatment, cost-effectiveness

Introduction

Malaria epidemics are increasingly frequent, and, at least in sub-Saharan Africa, tend to occur in populations already made vulnerable by poverty, malnutrition and/or armed conflict (Kiszewski & Teklehaimanot 2004). Past research on malaria epidemics has largely focussed on forecasting and early detection. By contrast, there is very little evidence on appropriate operational responses once epidemics do occur (Worrall *et al.* 2004). The World Health Organization (WHO) currently recommends prioritising case management, and providing free, highly efficacious artemisinin-based combination therapy (ACT) from the start at all levels of care (WHO 2004).

As regards diagnosis, WHO guidelines contemplate presumptive antimalarial treatment of all febrile patients. Under this strategy, diagnostic sensitivity is maximised (i.e. almost all cases are detected), and the case management algorithm is greatly simplified, facilitating the rapid decentralisation of care to the most peripheral levels, where community health workers (CHWs) may be entirely in charge of diagnosis and prescription (WHO 2004).

Presumptive treatment, however, has serious disadvantages because of its very poor specificity (many fever cases will

be considered as malaria even though they have a different pathology). This can, depending on the prevalence of malaria among febrile patients, lead to significant misdiagnosis and over-treatment. Over-treatment, in turn, increases drug costs; creates favourable conditions for the emergence of resistant strains; and leaves non-malaria patients without the drugs they need, and with a false perception of cure, which could delay their recourse to alternative therapies in case symptoms persist or worsen (Amexo *et al.* 2004).

Highly sensitive and specific rapid *Plasmodium falciparum* rapid diagnostic tests (RDTs) are available, and, given their ease of use and interpretation, could potentially be deployed at the peripheral level in epidemics, given a minimal degree of training, logistics and quality assurance (WHO 2003). From the financial standpoint, the public health improvement inherent in RDT deployment might result either in additional expenditures (due to the cost of testing) or significant savings (due to reduced use of expensive ACT drugs). Here, we present a cost-effectiveness analysis of RDT-supported *vs.* presumptive diagnosis in malaria epidemics where ACT is used.

This work is based on the experience of the medical non-governmental organisation Médecins Sans Frontières (MSF) during two recent malaria emergency interventions in southern Sudan, where 76 400 patients were treated over 6 months (Checchi 2004), and in Ethiopia, where 21 340 patients were treated over 4 months (Priotto 2003) (corresponding reports are freely available from the authors). In both sites, both RDTs and presumptive diagnosis were used at varying times in the epidemiological curve, and in different facilities, including peripheral health units.

Methods

Context

We considered a hypothetical *P. falciparum* epidemic context in a sub-Saharan Africa country, where poor access to formal health care structures leads to the establishment of temporary malaria treatment centres, operated at the peripheral level by relatively unskilled CHWs, and offering free treatment for uncomplicated malaria only. Treatment consists of ACT, quinine for pregnant women for whom ACT is contra-indicated and paracetamol.

Within this context, we compared two diagnostic and treatment strategies: (i) a presumptive strategy in which all patients with fever or a history of fever receive antimalarial, and (ii) an RDT-based strategy in which all patients with fever or a history of fever are tested by the Paracheck-Pf® test (Orchid Biomedical Systems, India), and receive antimalarial only if they are test-positive. Paracheck-Pf® is an RDT detecting the *P. falciparum* Histidine Rich Protein 2 antigen.

We did separate analyses for two ACT scenarios: artesunate plus amodiaquine (AS + AQ) and the more expensive artemether-lumefantrine or Coartem™ (ART-LUM). We chose these combinations because they are currently prioritised by the WHO for use throughout Africa. Both are available in blister form, but currently only ART-LUM is a fixed combination (i.e. both drugs are contained within one tablet).

Parameter inputs

Population profile. The posology of ACT is dependent on the patient's weight (ART-LUM) or age (AS + AQ): ACT costs would thus be greatly affected by the age distribution of fever and/or malaria infection. In addition, ACT is contra-indicated in the first trimester (AS + AQ) or throughout pregnancy (ART-LUM), and quinine is generally prescribed instead. For these reasons, we needed to make assumptions about the age and pregnancy status profile of our model population of febrile patients. Specifically, we had to determine (i) the proportion of patients that would fall within the dosage categories specified by current AS + AQ (Sanofi-Aventis) and ART-LUM (Novartis) blister packs (Table 1), and (ii) the proportion of patients who would be treated with quinine instead because of pregnancy.

In classical epidemics, host susceptibility to malaria is high irrespective of age and pregnancy status, and asymptomatic infections are rare (Kiszewski & Teklehaimanot 2004): based on these considerations, we assumed for our main analysis that (i) the age and pregnancy status distribution of febrile patients (see Population profile, Table 1) would resemble that in the general sub-Saharan African population (US Census Bureau 2004), (ii) the prevalence of malaria infection would be uniform across age groups and unaffected by pregnancy status and (iii) fever accompanied by a positive RDT result would equate to true symptomatic malaria.

Furthermore, we assumed that CHWs would be unable to distinguish new from repeat visits, and would thus treat each patient as a novel case (i.e. prescribe only first-line regimens).

Cost inputs. We calculated costs in Euros (as of August 2004, 1 Euro = 1.219 USD) per 10 000 febrile patients consulting in a period of 1 month (Table 1). This unit rate seemed appropriate, as it allowed us to factor in time-dependent costs (such as salaries), and since caseload is actually far higher in most serious epidemics (WHO 1998). Items and their values were extracted from MSF Sudan and Ethiopia operational accounts (reporting actual expenditures), or supplied by MSF's procurement agency

Table 1 Parameter inputs

1. Population profile	Proportion (uncertainty)	Notes on uncertainty
Malaria prevalence	(0–100%)	
Age/pregnancy distribution: AS + AQ scenario		
<7 years	21% (up to 39%)	Relative risk of fever (RR) up to 3.0
7–13 years	19% (up to 23%)	RR up to 2.0
>13 years	59% (as low as 36%)	Reference group
Pregnant (first trimester)	1% (up to 2%)	RR up to 3.0
Weight/pregnancy distribution: ART-LUM scenario		
<15 kg (<4 years)	12% (up to 22%)	RR up to 3.0
15–24 kg (4–7 years)	12% (up to 19%)	RR up to 2.5
25–34 kg (8–11 years)	11% (up to 14%)	RR up to 2.0
≥35 kg (≥12 years)	62% (as low as 39%)	Reference group
Pregnant (all trimesters)	3% (up to 6%)	RR up to 3.0

2. Cost inputs	Quantity	Unit cost (uncertainty)	Notes
2. a Biomedical costs	*Per test or treatment*		Costs include 3% freight
RDTs	1 Paracheck kit 1 pair of gloves	0.53 (as low as 0)	
Drugs: AS + AQ scenario			
<7 years	1 AS + 1 AQ × 3 days 0.9 PC × 2 days	0.43	Quantities refer to daily tablets of AS, AQ, QN (quinine) or paracetamol (PC) × number of days (d).
7–13 years	2 AS + 2 AQ × 3 days 3 PC × 2 days	0.81	
>13 years	4 AS + 4 AQ × 3 days 6 PC × 2 days	1.61	Within the <7 years group there are two dosage categories, but only one pack (caregivers of small children must split tablets)
Pregnant (first trimester)	6 QN × 7 days 6 PC × 2 days	1.51	
Drugs: ART-LUM scenario			
<15 kg (<4 years)	2 ART-LUM × 3 days 0.6 PC × 2 days	0.89	Quantities refer to daily co-formulated tablets of ART-LUM, plus quinine and paracetamol as above.
15–24 kg (4–7 years)	4 ART-LUM × 3 days 1.2 PC × 2 days	1.45	
25–34 kg (8–11 years)	6 ART-LUM × 3 days 3 PC × 2 days	1.89	
≥35 kg (>11 years)	8 ART-LUM × 3 days 6 PC × 2 days	2.38	
Pregnant (all trimesters)	6 QN × 7 days 6 PC × 2 days	1.51	
2. b Other costs	*Per 10 000 patients per month*		
CHWs	Presumptive: 32 RDT-based: 48	136 (0.5 to 2 times)	
Supervisors	Presumptive: 2 RDT-based: 2	875 (0.5 to 2 times)	
Drivers	Presumptive: 4 RDT-based: 5	171 (0.5 to 2 times)	
Vehicle rental and fuel	Presumptive: 4 RDT-based: 5	1555 (0.5 to 2 times)	

3. Effectiveness inputs	Percent	Notes
Sensitivity		Estimates of RDT sensitivity and specificity are the average of manufacturer specifications and the following studies: (Proux *et al.* 2001; Guthmann *et al.* 2002; Huong *et al.* 2002; Singh *et al.* 2002)
Presumptive strategy	100%	
RDT-based strategy	95%	
Specificity		
Presumptive strategy	0%	
RDT-based strategy	94%	

(MSF Logistique, Bordeaux, France). Costs are thus typical of what an international non-governmental relief organisation would incur. For simplicity's sake, items that accounted for negligible budget contributions (less than 1%) were excluded. We did not include costs of training on RDT use.

Based on programmatic data from southern Sudan and Ethiopia, we calculated that each treatment centre would consist of a team of two (presumptive strategy) or three (RDT-based strategy) CHWs working 4 days a week, 6 h a day, with a turnover of 10 min per consultation (i.e. 625 consultations per month per team, or 32 CHWs per 10 000 patients per month under the presumptive strategy and 48 under the RDT-based strategy). The programme would be supervised by two coordinators, and supported by vehicles and drivers at a ratio of one per 10 CHWs.

Effectiveness inputs. We looked at effectiveness from the standpoint of diagnosis of true symptomatic malaria among febrile patients. We assumed that the Paracheck RDT would be highly sensitive and specific, while presumptive diagnosis would have had perfect sensitivity and zero specificity (Table 1). Our main effectiveness measure was the number of false positives averted.

Data analysis

Main cost-effectiveness analysis. We used TreeAge Pro Suite 5.1 software (Tree Age Inc., Williamstown, MA, USA) to construct and analyse our model. As the main public health advantage of introducing RDTs would be to minimise over-treatment, we adopted as our primary cost-effectiveness outcome the incremental cost per false positive treatment averted. This indicator represents the added cost to the programme if one wished to prevent one unit case of over-treatment by using RDTs instead of presumptive diagnosis. This is an incremental cost-effectiveness ratio, and takes the following form:

$$\text{incremental cost/false positive averted} = \frac{\text{cost of RDT-based strategy-cost of presumptive stragey}}{\text{false positive averted by RDT-based strategy}},$$

where the number of false positives averted is given by the total number of non-malaria cases times the RDT's specificity. The incremental cost tends to increase if the RDT-based strategy costs significantly more than presumptive diagnosis, and decrease if RDTs prevent a great number of false positives. A negative incremental cost implies that the RDT-based strategy is 'dominant', namely costs less and is more effective.

As secondary cost-effectiveness outcome, we calculated the cost per true positive malaria case treated, expressed as:

$$\text{cost/true malaria case treated} = \frac{\text{cost of strategy}}{\text{number of true positives detected}},$$

where the number of true positives detected is given by the number of true malaria cases times the strategy's sensitivity.

We also calculated overall costs of the two strategies per unit of 10 000 febrile patients per month (these however do not include costs of drugs to treat non-malaria fever cases, since they are unrelated to our effectiveness measure).

Sensitivity analyses. Along with comparing the two strategies at different levels of malaria 'prevalence' (defined here as the proportion of true malaria cases among all fever cases), we did sensitivity analyses to observe the effect on cost-effectiveness outcomes of uncertainty in certain parameters (Table 1). These parameters were (i) the age and pregnancy status distribution of patients: contrary to our initial assumption, we hypothesised that younger individuals and pregnant women would experience higher rates of fever due to malaria or other illnesses, or present more often to health centres and would thus be overrepresented among the population of febrile patients (Theander 1998; Boisier *et al*. 2002); (ii) the price of the RDT test, assuming a future price reduction; (iii) the total non-biomedical costs (i.e. excluding drugs and RDTs), assuming up to twofold inter-country differences due to variation in salaries, transportation and other logistics costs (MSF Logistique, personal communication). We did not conduct a sensitivity analysis of the price of ACT, as AS + AQ and ART-LUM seemed to provide realistic lower and upper-end estimates of foreseeable future prices.

Tolerance in incremental costs. Policy decisions might be based not merely on whether a strategy is likely to be cost-effective, but rather on whether an overall financial and/or public health benefit of this strategy could be achieved if the decision maker were prepared to tolerate an additional expenditure. For this reason, we also compared the two strategies assuming that financing bodies would be willing to tolerate an incremental cost of up to 1 € or 2 € per false positive averted.

Results

Main cost-effectiveness analysis. As malaria prevalence increases, the difference in cost (per 10 000 fever consultations per month) between the presumptive and

RDT-based strategies becomes more substantial: Table 2 illustrates this for low (25%), medium (50%) or high (75%) values of malaria prevalence. The threshold prevalence above which the RDT-based strategy becomes more expensive is 21% in the AS + AQ scenario, and 55% in the ART-LUM scenario (data not shown). However, cost differences are relatively modest (Table 2), and even at a very high prevalence (90%), only +30% (€ 32 634 *vs.* € 25 108) for AS + AQ, and +19% (€ 39 525 *vs.* € 33 112) for ART-LUM.

The incremental cost per false positive case averted increases exponentially with prevalence, and varies considerably according to the ACT used. As above, when prevalence exceeds 21% (AS + AQ) or 55% (ART-LUM) (Figure 1a,b), preventing a case of over-treatment through RDTs entails a positive incremental cost. Conversely, below these prevalences the RDT-based strategy results in lower costs, i.e. is dominant. However, if the financing body is willing to tolerate an incremental cost of up to 1 € per false positive averted, these prevalence thresholds become 58% (AS + AQ) and 70% (ART-LUM), meaning the RDT-based strategy is favoured in a wider range of possible prevalence scenarios. At the above prevalence thresholds, a tolerance of 1 € equates to a difference in total costs of less than +16% (€ 29 190 *vs.* € 25 108) for AS + AQ, and +9% (€ 35 948 *vs.* € 33 112) for ART-LUM. The thresholds rise further (though less considerably) if tolerance is up to 2 €.

Sensitivity analyses. If the unit cost of a Paracheck kit is cut by half (to € 0.27), the RDT-based strategy is dominant up to prevalence thresholds of 45% for AS + AQ and 68% for ART-LUM (Figure 2a,b). If, in addition, incremental cost tolerance up to 1 € per false positive averted is introduced, these thresholds increase substantially (up to 70%) for AS + AQ, but modestly (up to 78%) for ART-LUM. Doubling tolerance to 2 € does not greatly affect thresholds.

Cost-effectiveness is less sensitive to variation in the age and pregnancy distribution of the febrile patient population (Figure 3a,b). However, in the AS + AQ scenario the presumptive strategy becomes dominant at even zero malaria prevalence when the relative proportion of young children and pregnant women is greatest (Table 1).

Inter-country variation in non-biomedical costs strongly affects the strategy comparison (Figure 4a,b): in the AS + AQ scenario, presumptive treatment is the dominant choice at any malaria prevalence if only these costs were 1.6 times higher than the amount we estimated.

Discussion

In this cost-effectiveness analysis considering a malaria epidemic situation in which ACT is used at the peripheral level of care, we could not demonstrate a clear-cut cost-effectiveness superiority of either presumptive diagnosis or an RDT-based strategy, mainly due to the dynamic nature of prevalence during an epidemic. Nevertheless, given the current price of most rapid tests and ACT, the RDT-based strategy would avoid much over-treatment, and greatly improve management of non-malaria fever cases, with only

Table 2 Cost-effectiveness outcomes at three different levels of malaria prevalence

	Prevalence = 25%		Prevalence = 50%		Prevalence = 75%	
	Presumptive strategy	RDT-based strategy	Presumptive strategy	RDT-based strategy	Presumptive strategy	RDT-based strategy
Fever cases	10 000	10 000	10 000	10 000	10 000	10 000
True malaria cases	2500	2500	5000	5000	7500	7500
True cases detected	2500	2375	5000	4750	7500	7125
False negatives	0	125	0	250	0	375
False positives	7500	450	5000	300	2500	150
False positives averted	0	7050	0	4700	0	2350
AS + AQ scenario						
Total cost (€)	25 108	25 638	25 108	28 329	25 108	31 019
Cost difference (%)	–	+2%	–	+13%	–	+24%
Cost/true malaria case detected (€)	10.0	10.8	5.0	6.0	3.3	4.4
Incremental cost/false positive averted (€)	–	+0.1	–	+0.6	–	+2.5
ART-LUM scenario						
Total cost (€)	33 112	27 900	33 112	32 371	33 112	36 842
Cost difference (%)	–	−16%	–	−2%	–	+11%
Cost/true malaria case detected (€)	13.2	11.7	6.6	6.8	4.4	5.2
Incremental cost/false positive averted (€)	–	−0.7	–	−0.2	–	+1.6

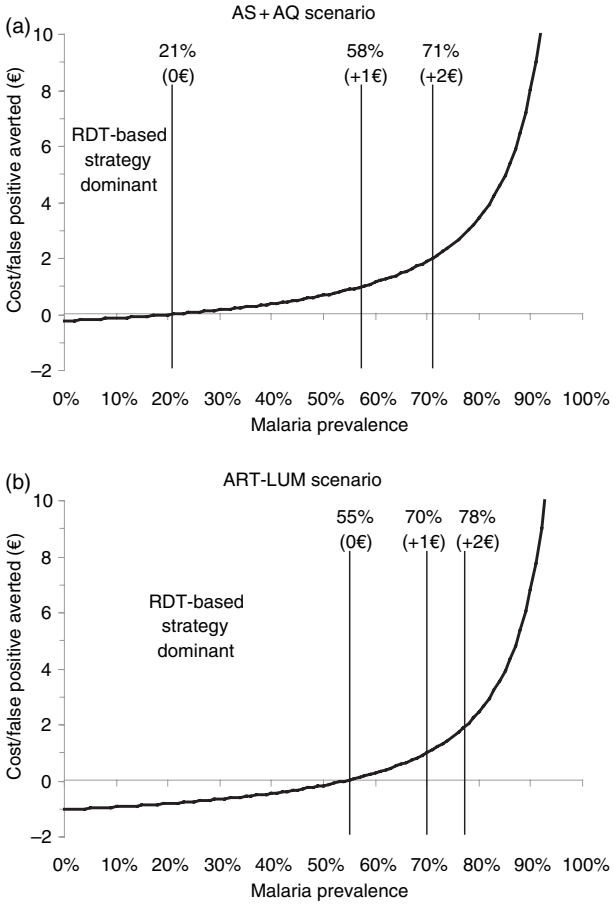

Figure 1 a,b Incremental cost per false-positive treatment averted, as a function of malaria prevalence (AS + AQ scenario and ART-LUM scenario). Vertical bars indicate prevalence thresholds (%) below which the RDT-based strategy is cost-effective, according to whether the decision maker tolerates an incremental cost per false positive averted of 0 €, up to 1 €, or up to 2 €.

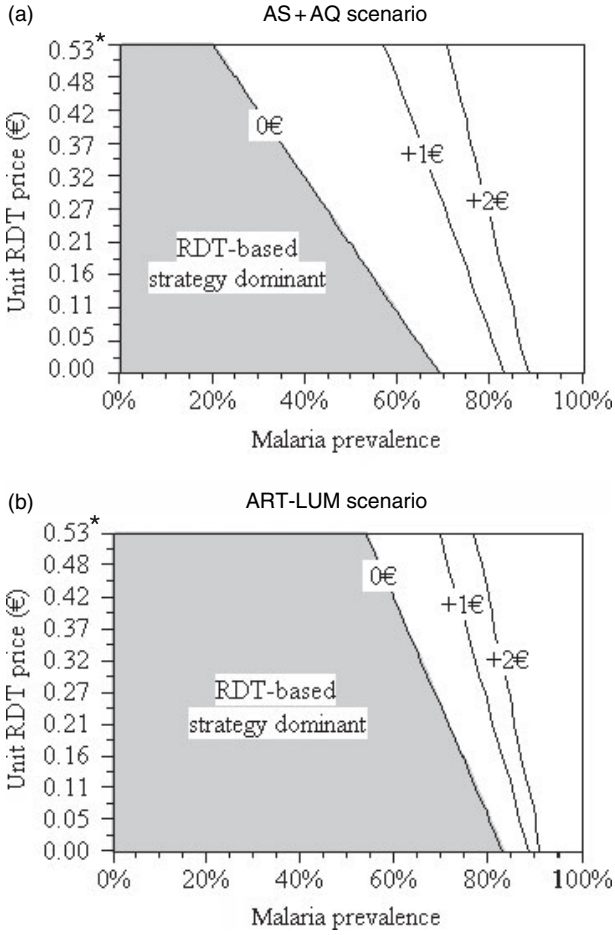

Figure 2 a,b Sensitivity analysis of RDT price: incremental cost per false-positive treatment averted, as a simultaneous function of unit test price (*Y*-axis) and malaria prevalence (*X*-axis) (AS + AQ scenario and ART-LUM scenario). Diagonal lines represent different levels of incremental cost tolerance. In a scenario of zero cost tolerance, the RDT-based strategy is dominant at any combination of RDT price and malaria prevalence that falls in the grey area. If tolerance is increased, the decision favours RDTs at even higher prices or malaria prevalences (all combinations to the *left* of the respective tolerance line). *indicates value in main analysis.

a moderate cost increase. Indeed, our results suggest that if financing bodies were willing to tolerate an added cost of up to 1 € per false positive averted (namely a total cost increase of less than 20%), RDTs would be favoured in a majority of scenarios. Even higher tolerance, however, might not bring about substantial added benefits. Unit test price is a major determinant of the cost-effectiveness of RDTs.

The evolution of prevalence in the course of a malaria epidemic may largely determine which strategy would be more cost-effective if used consistently. If the epidemic peak were sustained over most of the intervention period, presumptive diagnosis would be more cost-effective overall, whereas a shorter peak followed by progressively declining prevalence would favour RDTs. Timing of RDT introduction with respect to the epidemic peak would also be important. Here we presented a comparison for only 1 month of intervention. If better data on the typical evolution of malaria epidemics were collected, the analysis could be extended to the entire epidemic period. It should be noted here that malaria prevalence in the general population might not accurately reflect prevalence among fever cases presenting for treatment. The latter indicator would be affected not only by malaria transmission, but

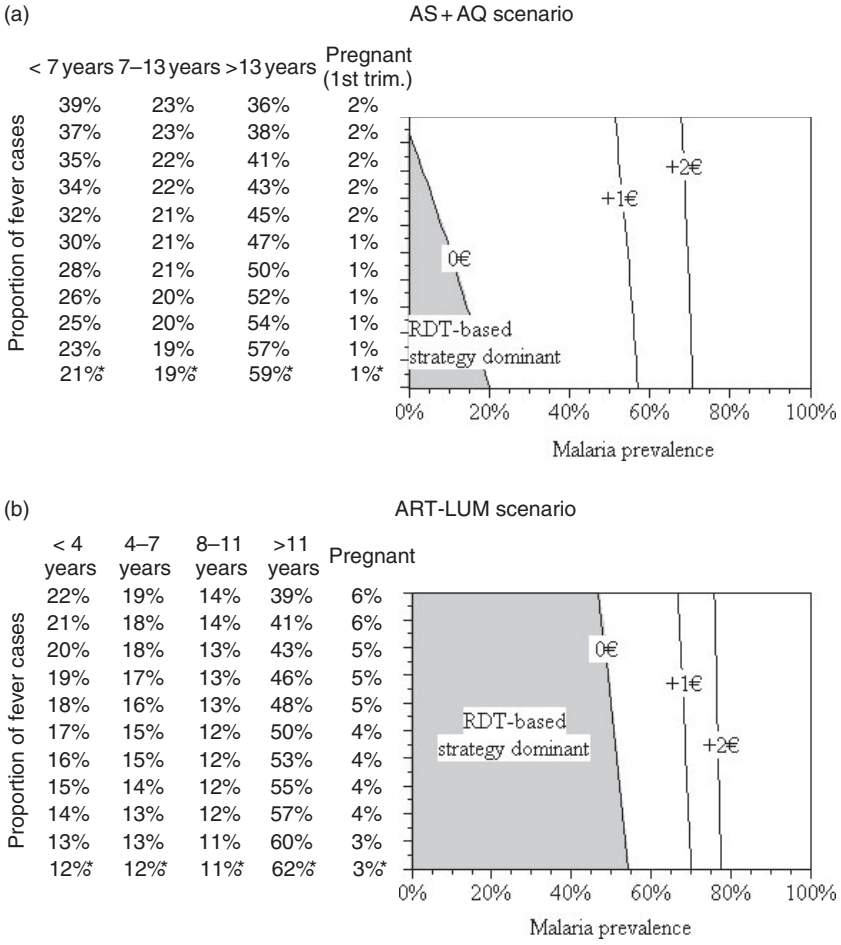

Figure 3 a,b Sensitivity analysis of age and pregnancy status distribution: incremental cost per false-positive treatment averted, as a simultaneous function of variation in age and pregnancy distribution of febrile patients (*Y*-axis) and malaria prevalence (*X*-axis) (AS + AQ scenario and ART-LUM scenario). Diagonal lines represent different levels of incremental cost tolerance. Towards the top of the graph, children and pregnant women are over-represented among fever cases, whereas towards the bottom the age and pregnancy distribution of fever cases resembles that in the general population (i.e. our initial assumption). *indicates value in main analysis.

also by the incidence of other febrile illnesses, and by care seeking patterns. It should therefore be measured separately for cost-effectiveness purposes. In Ethiopia (2003), southern Sudan (2003) and Burundi (2000), 64, 60 and 80% of fever cases were RDT-positive at epidemic peak (MSF unpublished data). Rapid surveys of fever patients could inform the strategy decision during future epidemics: when proportionate malaria morbidity surpasses the predicted cost-effectiveness threshold, RDT use could be suspended.

As expected, RDTs are much more cost-effective if the more expensive ART-LUM regimen is used, rather than AS + AQ. Cost-effectiveness is not strongly affected by variation in the age and pregnancy profile of the patient population; however, a scenario in which children or pregnant women are overrepresented among fever cases (probably typical of some emergency programmes targeting these groups especially, or of semi-immune settings where non-pregnant adults are less susceptible to symptomatic malaria) does favour presumptive treatment, since drug costs decrease. Conversely, the cost-effectiveness of RDTs is greatly increased as their price declines. The strategy comparison is also very sensitive to inter-country variation in non-biomedical programme costs. We calculated these costs based on MSF programmatic experience: however, costs might well be higher or lower depending on the set up of treatment programmes implemented in other contexts.

It should be noted that our comparison of total expenditures under the two strategies does not take into account costs of drugs used to treat non-malaria fevers, since we only considered malaria-specific treatment centres and looked at an effectiveness outcome strictly related to malaria diagnosis.

In epidemic settings where access to health care may be poor, the public health advantages of more specific diagnosis should be weighed carefully against the dangers of reduced sensitivity. However, febrile illnesses incorrectly diagnosed and treated only as malaria in a presumptive

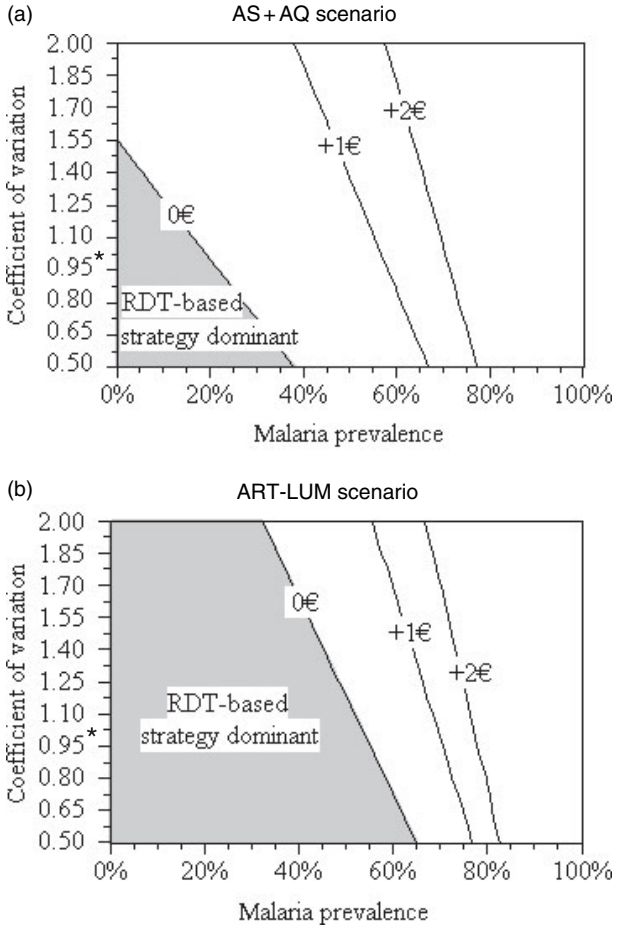

Figure 4 a,b Sensitivity analysis of inter-country variation in non-biomedical costs: incremental cost per false-positive treatment averted, as a simultaneous function of variation in non-biomedical costs (*Y*-axis) and malaria prevalence (*X*-axis) (AS + AQ scenario and ART-LUM scenario). Diagonal lines represent different levels of incremental cost tolerance. *indicates value in main analysis.

scenario would also be at risk of aggravation and death. Their case-fatality ratio (CFR) would depend on the proportionate aetiology of such fevers in any setting or season.

In short, there is a balance between the harms of malaria cases missed due to imperfect RDT sensitivity and the benefits of better management of non-malaria fevers. This harm-benefit balance would favour presumptive treatment if the malaria treatment programme were implemented vertically in a setting with little other access to health care, and RDT use if alternative treatment for non-malaria febrile illnesses were available. We illustrate this roughly in Table 3 for children under 5, where we calculate the net benefit (as deaths averted and hospital cost savings per false positive diagnosis averted) of RDTs in two scenarios of low (25%) and high (75%) access to outpatient and inpatient health care, and hypothesizing a 50% malaria prevalence. Here, we assume conservatively that, out of all non-malaria fever cases, only 50% would be due to potentially fatal acute respiratory infections (ARI), while the rest would be self-limiting (in reality other potentially fatal aetiologies, such as febrile diarrhoeas, could occur). The RDTs would probably save lives due to better ARI management, and result in a hospital cost saving of 0.6 € per false positive averted in a scenario of good health access (Table 3). This saving is close to our proposed tolerance level of 1 €, demonstrating that such an additional expenditure may be ultimately justifiable on cost-benefit, if not strictly cost-effectiveness, grounds. In the long-term, prevention of drug resistance represents an additional financial and public health benefit further tipping the balance towards RDTs. However, the future impact of drug pressure on parasite sensitivity to ACT combinations (especially ART-LUM), for which potential resistance mechanisms are only now being elucidated, is unknown: the corresponding benefit per unnecessary treatment averted by RDTs is thus hard to predict.

Much would also depend on the quality of RDT handling and use. Based on published evidence, we assumed near-ideal RDT effectiveness. Post-implementation studies of RDT use, however, would be helpful to obtain more likely estimates of these tests' accuracy in routine African conditions (Premji *et al.* 1994). It is also likely that better diagnosis would considerably reduce indirect costs to both consumer and provider because of shorter illness, decreased re-visits, and less recourse to treatments for severe conditions. These costs were not included in our analysis, but have been estimated to account for as much as 80% of total (Breman *et al.* 2004).

Our findings are probably not applicable to stable malaria settings, where the assumption 'fever plus test-positivity = malaria' would not be appropriate due to frequent asymptomatic infections, especially among adults. In such settings, a better comparison would be between presumptive treatment and an RDT-supported clinical algorithm aiming to maximise both positive and negative predictive values. Furthermore, microscopy should be included among the diagnosis options in stable contexts.

The RDT use in malaria epidemics may be constrained by several factors, such as insufficient human resources and training capacity, and inadequate procurement, transport and stocking procedures and logistics (Bualombai *et al.* 2003). Nevertheless, we feel that, as in other malaria-related issues today, the right health economics question to ask is not only whether a proposed intervention is likely to

Table 3 Calculation of net benefits of RDTs over presumptive strategy (= excess deaths averted and hospital costs saved) among children under 5, based on 10 000 fever cases, a malaria prevalence of 50% and a proportion of potentially fatal ARI cases of 50% among all non-malaria fever cases. 'Health access' means proportion of (severe or non-severe) cases obtaining care. Sensitivity and specificity of strategies are as in Table 1. Other parameters implied in calculations are: (i) per cent of untreated malaria cases becoming severe = 5% (Goodman *et al.* 1999), (ii) severe malaria CFR if treated = 19.2% (Goodman *et al.* 2000), (iii) severe malaria CFR if untreated = 50% (Goodman *et al.* 2000), (iv) percent of untreated ARI cases becoming severe = 9.2% (Rudan *et al.* 2004), (v) percent of treated ARI cases becoming severe = 4.6% [based on 50% reduction in mortality risk if treated promptly; (Enarson *et al.* 2005)], (vi) severe ARI CFR if treated = 9.9% (Rudan *et al.* 2004), (vii) severe ARI CFR if untreated = 40% [based on pre-antibiotic era; (Graham 2002)], (viii) cost to health system of one hospital stay = € 52.3 [based on typical stay of 4.5 days; (Goodman *et al.* 2000)]

	Health access = 25%		Health access = 75%	
	Presumptive strategy	RDT-based strategy	Presumptive strategy	RDT-based strategy
Harm: excess malaria deaths and malaria hospitalisation costs due to false negatives missed by RDTs				
Malaria cases missed and left untreated (false negatives)	0	250	0	250
Untreated malaria cases becoming severe	0	13	0	13
Severe cases receiving inpatient treatment	0	3	0	9
Treated or untreated severe cases dying (d_m)	0	5	0	3
Total cost of inpatient malaria treatment (€) (C_m)	0	163	0	490
Benefit: less ARI deaths and ARI hospitalisation costs due to false positives averted by RDTs				
Non-malaria fever cases detected (false positives averted) (a)	0	4700	0	4700
ARI cases	2500	2500	2500	2500
ARI cases wrongfully treated as malaria	2500	150	2500	150
ARI cases not wrongfully treated and receiving further outpatient treatment for ARI†	0	588	0	1763
ARI cases (treated or untreated) becoming severe	230	203	230	149
Severe ARI cases receiving inpatient treatment	58	51	173	112
Treated or untreated severe ARI cases dying	75	66	40	26
Total deaths averted (d_a)		9		14
Total cost of inpatient ARI treatment (€)	3005	2652	9014	5837
Total cost saving (€) (C_a)	–	353	–	3177
Net benefit:				
Total deaths averted through RDT strategy ($=d_a-d_m$)	–	4	–	11
Total hospital cost saving (€) ($S = C_a-C_m$)	–	190	–	2688
Hospital cost saving per false positive averted (€) ($= S/a$)	–	0.04	–	0.6

†We assume that non-malaria ARI cases that *are* wrongfully treated with ACT will not visit a second source of outpatient care. They may however, seek inpatient care if they aggravate.

be cost-effective, but, rather, what benefits can be achieved if financing bodies are willing to tolerate higher spending, as seems unavoidable to give Roll Back Malaria a chance of success. Our analysis contributes to answering this question by indicating broadly the financial implications decision makers should expect if the choice were taken to deploy RDTs in malaria epidemics. Interestingly, decreased test prices would make the RDT strategy much more cost-effective: along with securing lower ACT prices, international campaigns should therefore also aim for more affordable diagnostics.

We recommend that this analysis be extended to non-epidemic settings with more complex treatment options and host susceptibility patterns, and that better data be gathered to inform parameter input, especially as regards the clinical and economic consequences of misdiagnosis. While such evidence is missing, we believe based on our findings that decision makers adopting a 'do no harm' principle should, despite a (relatively small) added cost, strongly consider RDT use throughout or during part of a malaria epidemic, where this is feasible given local human resources and logistics conditions.

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Réponse opérationnelle aux épidémies de malaria: les tests de diagnostic rapides ont-ils un bon rapport coûts-efficacité?

OBJECTIF Comparer le rapport coûts-efficacité du traitement de la malaria basé sur le diagnostic présomptif à celui du traitement basé sur l'utilisation des tests de diagnostic rapides (TDRs).
MÉTHODES Nous avons calculé les coûts directs (basés sur l'expérience de l'Ethiopie et du sud du Soudan) et l'efficacité (en terme de réduction du surtraitement) d'un programme de traitement gratuit et décentralisé utilisant l'artésumate plus l'amodiaquine (AS+AD) ou l'artemether-lumefantrine (ART-LUM) dans une épidémie à *Plasmodium falciparum*. Notre principale mesure du rapport coûts-efficacité était le coût incrémental par traitement d'un faux positif identifié par les TDRs.
RÉSULTATS Alors que la prévalence de la malaria augmente, la différence dans les coûts entre les traitements basés sur la présomption et les TDRs augmentent également. Le seuil de prévalence au-delà duquel les stratégies basées sur les TDRs deviennent plus coûteuses est de 21% dans le scénario AS+AQ et 55% dans celui du ART-LUM. Mais, ces seuils augmentent à 58% et 70% respectivement lorsque le corps financier tolère un coût incrémental de 1€ par faux positifs évités. Toutefois, même dans une prévalence élevée (90%) de malaria dans le cas d'un pique d'épidémie, une stratégie basée sur les TDRs coûterait modérément plus que la stratégie présomptive: +29,9% dans le scénario AS+AQ et +19,4% dans celui de l'ART-LUM. La comparaison des traitements est peu influencée par la distribution de l'âge et des grossesses dans les cas de fièvres. Mais, elle est fortement affectée par les variations dans les coûts non biologiques. Si les prix à l'unité des TDRs étaient réduits de moitié ils auraient un bon rapport coûts-efficacité dans une prévalence de malaria allant jusqu'à 45% dans le cas du traitement a l'AS+AQ et jusqu'à 68% dans le traitement a l'ART-LUM.
CONCLUSION Dans la plupart des scénarios de prévalence d'épidémie, les TDRs réduiraient considérablement le surtraitement avec seulement une augmentation modérée des coûts par rapport au diagnostic présomptif. Une diminution substantielle du prix unitaire des TDRs augmenterait énormément leur rapport coûts-efficacité et ils devraient alors être recommandés. La tolérance d'un coût incrémental de 1 € est probablement justifiée au vu de la santé publique en générale et des bénéfices financiers. Les TDRs devraient être considérées pour les épidémies de malaria si les ressources logistiques et humaines le permettent.

mots clés *Plasmodium falciparum*, malaria, épidémique, test de diagnostic rapide, traitement présomptif, coûts-efficacité

Respuesta operativa a epidemias de malaria: ¿'son costo-efectivos los test de diagnóstico rápido?

OBJETIVO Comparar la costo-efectividad del tratamiento de malaria, basado en un diagnóstico presuntivo, con el tratamiento de malaria basado en un test diagnóstico rápido (TDRs).
MÉTODOS Calculamos los costes directos (basados en experiencias en Etiopía y el sur de Sudán) y la efectividad (en términos de reducir el sobre-tratamiento) de un programa de tratamiento gratis y descentralizado, utilizando artesunato más amodiaquina (AS+AQ) o artemeter-lumefantrina (ART-LUM) en una epidemia de *Plasmodium falciparum*. Nuestra principal medida de costo-efectividad fue el coste incremental por cada tratamiento de un falso positivo prevenido por TDRs.
RESULTADOS A medida que aumenta la prevalencia de malaria, la diferencia entre el costo del tratamiento presuntivo y aquel basado en TDRs aumenta. La prevalencia umbral, por encima de la cual la estrategia basada en diagnóstico por TDRs se convierte en más cara, es del 21% en el caso de AS+AQ y del 55% para ART-LUM. Estos umbrales aumentan a 58% y 70% respectivamente si el financiador tolera un coste incremental de 1 € por falso positivo prevenido. Sin embargo, aún con una alta prevalencia (90%) de malaria, consistente con un pico epidémico, una estrategia basada en TDRs solo costaría moderadamente más que la estrategia de tratamiento presuntivo: +29.9% en el escenario de AS+AQ y +19.4% para ART-LUM. La comparación del tratamiento es insensible a la distribución de edad y embarazos de los casos febriles, pero está muy afectada por la variación de costes no-biomédicos. Si el precio de la unidad fuese la mitad, los TDRs serían más costo efectivos con una prevalencia de malaria de hasta un 45% en el caso del tratamiento con AS+AQ y con una prevalencia de hasta un 68% para el tratamiento con ART-LUM.
CONCLUSIÓN En la mayoría de los escenarios epidémicos, los TDRs reducirían considerablemente el sobre-tratamiento con solo un incremento moderado de los costes sobre el diagnóstico presuntivo. Una disminución sustancial en el precio de los TDRs aumentaría enormemente su costo-efectividad, y se debería por lo recomendar. Un coste incremental tolerado de 1 € está probablemente justificado, dados los beneficios financieros y de salud pública en general. Los TDRs deberían considerarse en epidemias de malaria, si los recursos logísticos y humanos lo permiten.

palabras clave *Plasmodium falciparum*, malaria, epidemia, test diagnóstico rápido, tratamiento presuntivo, costo efectividad