

Cost-effectiveness of malaria intermittent preventive treatment in infants (IPTi) in Mozambique and the United Republic of Tanzania

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Objective To estimate the cost-effectiveness of malaria intermittent preventive treatment in infants (IPTi) using sulfadoxine-pyrimethamine (SP).

Methods In two previous IPTi trials in Ifakara (United Republic of Tanzania) and Manhica (Mozambique), SP was administered three times to infants before 9 months of age through the Expanded Programme on Immunization. Based on the efficacy results of the intervention and on malaria incidence in the target population, an estimate was made of the number of clinical malaria episodes prevented. This number and an assumed case-fatality rate of 1.57% were used, in turn, to estimate the number of disability-adjusted life years (DALY) averted and the number of deaths averted. The cost of the intervention, including start-up and recurrent costs, was then assessed on the basis of these figures.

Findings The cost per clinical episode of malaria averted was US\$ 1.57 (range: US\$ 0.8–4.0) in Ifakara and US\$ 4.73 (range: US\$ 1.7–30.3) in Manhica; the cost per DALY averted was US\$ 3.7 (range: US\$ 1.6–12.2) in Ifakara and US\$ 11.2 (range: US\$ 3.6–92.0) in Manhica; and the cost per death averted was US\$ 100.2 (range: US\$ 43.0–330.9) in Ifakara and US\$ 301.1 (range: US\$ 95.6–2498.4) in Manhica.

Conclusion From the health system and societal perspectives, IPTi with SP is expected to produce health improvements in a cost-effective way. From an economic perspective, it offers good value for money for public health programmes.

Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español.

Introduction

Malaria is one of the leading causes of morbidity in endemic countries. Between 350 and 660 million clinical episodes of the disease occur per year among African children,^{1,2} and roughly 1.2 million deaths (representing 2% of all premature deaths in the world) are caused annually by malaria in low- and middle-income countries,³ although estimates range from 700 000 to 2.7 million deaths per year.⁴ Of all global deaths due to malaria, around 75% are estimated to occur in African children.⁴

Current WHO recommendations for malaria control in children in endemic areas rely on case management, use of insecticide-treated nets and vector control,^{5,6} none of which has proved fully effective for controlling the infection.^{7–11} Hence, there is a need to test new strategies that, combined with existing interventions, can effectively reduce the burden of malaria among children in endemic areas.⁵

The delivery of intermittent preventive treatment in infants (IPTi) during routine contacts through the Expanded Programme on Immunization (EPI)^{12–14} is a promising malaria control strategy whose efficacy rates in the prevention of malaria episodes^{15–21} range from 22.6%¹⁶ to 63.2%.¹⁸

Cost-effectiveness analysis, which provides information that is crucial for policy recommendations for malaria control at both the national and international levels, can help guide the optimal allocation of health sector resources.^{22,23} To provide this information, we carried out a cost-effectiveness analysis based on the results of two very similar IPTi trials, one of which was undertaken in Ifakara, the United Republic of Tanzania, and the other in Manhica, Mozambique.^{16,18}

Methods

Study area and population

The trials are described in more detail elsewhere.^{16,18} The Tanzanian trial was based in Ifakara town (Kilombero district), whose population is 55 000. Malaria transmission is perennial, with two rainy seasons and a cool dry season from July to September. Sulfadoxine-pyrimethamine (SP) was the recommended first-line treatment for malaria during the study. Compliance with the routine EPI vaccination schedule was high, with 92% of children receiving three doses of diphtheria-tetanus-pertussis (DTP) vaccine plus oral poliovirus vaccine and 80% receiving measles vaccine. The rate of use of insecticide-treated nets was 70%.

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(Submitted: 6 February 2008 – Revised version received: 18 June 2008 – Accepted: 25 June 2008 – Published online: 6 January 2009)

The Mozambican study was based in Manhica (Maputo province), a town of 36 000 inhabitants in southern Mozambique with a subtropical climate, a warm rainy season from November to April, and a cool, dry season the rest of the year. Compliance with EPI vaccines is very high, as more than 95% of children receive all three doses of the combination vaccine against DTP, polio and hepatitis B, and more than 85% are vaccinated against measles. In both sites malaria transmission is mostly due to *Plasmodium falciparum*. Insecticide-treated nets are not used in the community.

Cost-effectiveness analysis

The cost-effectiveness analysis presented here follows standard cost-effectiveness methods.^{24–28} In cost-effectiveness analysis, the costs and outcomes of a new health intervention are compared with those of the currently practiced interventions and/or with doing nothing (no intervention). This enables the selection of competing interventions, based on their relative efficiency, to obtain better value for money in health spending and other benefits. To estimate the cost-effectiveness ratios of the IPTi intervention, the estimated aggregate effect of the IPTi intervention was divided by the estimated aggregate cost of providing the intervention for a reference target population of 1000 immunized infants.

The cost-effectiveness ratios presented are incremental and reflect a comparison of the IPTi intervention with a do-nothing alternative. They include the cost per malaria episode averted, the cost per disability-adjusted life year (DALY) averted,^{29–32} and the cost per malaria death averted. DALYs averted were calculated by combining the burden of disease averted due to less malaria morbidity (as a function of malaria incidence, disease duration and impact on quality of life) and less malaria mortality (as a function of malaria incidence, case-fatality rate and average life expectancy at age 1 year). Cost-effectiveness ratios are presented in United States dollars (US\$) for the year 2006.

Estimation of health impact

The IPTi intervention evaluated in this analysis included the delivery of single doses of SP up to three times during the first year of life, alongside routine EPI vaccinations.

The health effects used in the cost-effectiveness analysis were based on the efficacy results from the Ifakara and Manhica trials and on the incidence of malaria in these sites at the time of the trials.^{16,18} For the purposes of the economic evaluation, we used the total number of cases averted for a reference population of 1000 infants, based on the number of children enrolled in the trials who had received at least one dose of SP by 12 months of age.

The trial results showed a reduction in the incidence of all malaria episodes of 63.2% (95% confidence interval, CI: 44.2–74.6) in Ifakara¹⁸ and 22.2% (95% CI: 3.9–37.0) in Manhica.¹⁶ Neither study showed an increase in clinical episodes of malaria after discontinuation of IPTi (rebound effect).^{16,33} The malaria attack rates in the placebo group were 35.2% and 40.2% in the Ifakara and Manhica trials, respectively. The cost-effectiveness ratio was also calculated using the pooled efficacy of the six completed IPTi trials that compared SP with placebo, which has been estimated at 30.1% (range: 19.7–39.1) against all clinical malaria episodes.³⁴

Fewer malaria cases mean fewer malaria deaths. None of the IPTi trials conducted to date has been large enough to provide a direct estimate of the effect of the intervention on mortality. However, previous studies have shown that reducing malaria incidence does reduce mortality from the disease.³⁵ Case-fatality field data derived from hospital admissions only have revealed case-fatality rates (CFRs) for malaria in infants ranging from 4.7%³⁶ to 5.8%.³⁷ A recent epidemiological model based on field data yielded a case-fatality rate for malaria in infants of 1.57%,^{38,39} and that is the rate we employed in this study. Because hospitalized infants are more likely to have severe malaria episodes, it was considered more appropriate to use the lower rate of 1.57% to reflect the CFR for clinical episodes of all types. DALYs were calculated according to standard methods, excluding age weighting.^{40–42} For infant deaths, an average life expectancy of 51.35 years was used based on life tables for men and women in eastern Africa.⁴³

Intervention costs

We calculated both the financial (budgetary) and the non-financial costs of the IPTi intervention, which together comprised its economic costs. Non-financial

implications (opportunity costs) for resource use had to do, for instance, with the utilization of spare health system capacity or the switching of health resources from one use to another.

To calculate economic costs of the IPTi intervention, we took into account all costs involved in implementing it, including the costs of planning, delivery and monitoring. We also included all costs associated with policy change (strategy definition), sensitization (meetings with health sector stakeholders and district level health managers), behaviour change (communication to the population, staff training, intervention monitoring), the IPTi drug SP (import, purchase, storage and distribution), and drug administration (drug delivery, mothers' education, and filling out the health card).

Intervention costs were partially collected from the two trials. However, as the conditions surrounding neither trial reflected actual practice in terms of IPTi delivery and costs incurred, intervention costs were taken instead from a more recent cost study that was part of an IPTi community effectiveness trial conducted from 2005 to 2008 in the southern United Republic of Tanzania (Mtwara and Lindi regions), where Ifakara is also situated.⁴⁴ The cost data collected from the Mtwara and Lindi regions exclude research and other costs that are usually involved in clinical trials. Hence, they reflect the real costs of IPTi delivery in routine clinical practice in the southern part of the country. Given the similarities between Mozambique and the United Republic of Tanzania in per capita incomes and health service delivery, including EPI schedule, the cost data collected in Mtwara and Lindi regions were also considered the most appropriate for application in the Manhica study.⁴⁴ Only the price of SP was treated as different between the two sites.

IPTi intervention costs are presented in Table 1, with financial and non-financial costs presented separately. In the United Republic of Tanzania, the cost per dose of IPTi delivered was roughly US\$ 0.128. Of this amount, 60% comprised financial costs: US\$ 0.0536 per dose for training, US\$ 0.019 per dose for sensitization, and US\$ 0.0136 per dose for purchase of the drug (including wastage). An average dose of half a tablet of SP and an assumed wastage rate of 30% were

used to calculate the cost per dose, based on the price of the drug in 2006 in the Medical Stores Department (the agency responsible for bulk purchases of medicines and medical supplies) of the United Republic of Tanzania. In Mozambique the drug price used was US\$ 0.0375 per dose, and as a result the total cost per dose delivered (US\$ 0.1522) was higher in that country. As not all infants receiving the first dose receive the second and third doses, the IPTi intervention costs for the reference target of 1000 infants were adjusted for a drop-out rate of 4% from the first to the second dose in both sites, and of 19% and 15% from the second to the third dose for Ifakara and Manhiça, respectively. Hence, 77% of infants in Ifakara and 81% in Manhiça were presumed to receive three doses of SP.^{16,18}

Sensitivity analysis

Multivariate sensitivity analysis was performed using Monte-Carlo simulations generated by @Risk (version 4.5) add-in tool to Microsoft Excel® (Palisade Corporation, Ithaca, NY, USA) to explore the robustness of the results in the face of simultaneous variation in selected assumptions and data inputs. Cost-effectiveness ranges were generated stochastically by varying four key input parameters – IPTi efficacy, case-fatality rate, malaria attack rate and cost per dose of IPTi delivered – in 10 000 simulations. Efficacy ranges were defined by the 95% CI from the trials themselves, while for the other three variables the 95% confidence ranges were assumed. Efficacy distributions were assumed to be triangular.

Table 1. **Intervention costs per dose of SP delivered in Mozambique (Manhiça) and the United Republic of Tanzania (Ifakara) (2006 prices)**

Activity component	Health system level	Financial costs (US\$ cents)	Opportunity costs (US\$ cents)	Total costs (US\$ cents)
Planning and management of strategy change	National	0.01	0.02	0.03
Sensitization	District	0.76	1.12	1.88
Behaviour change communication	National	0.03	0.05	0.08
Drug distribution	National	1.50	0.00	1.50
Training	District	3.06	2.30	5.36
Administration of intervention in health facilities	District	0.00	1.25	1.25
Strategy management	National	0.65	0.10	0.75
	District	0.62	0.00	0.62
Drug purchase (United Republic of Tanzania only)	National	1.10	0.26	1.36
Drug purchase (Mozambique only)	National	3.49	0.26	3.75
Total (United Republic of Tanzania)	National	3.29	0.43	3.72
	District	4.44	4.67	9.11
	Overall	7.73	5.10	12.83
Total (Mozambique)	National	5.68	0.43	6.11
	District	4.44	4.67	9.11
	Overall	10.12	5.10	15.22

IPTi, intermittent preventive treatment in infants; SP, sulfadoxine-pyrimethamine.
Source: Ref. 44.

Results

Table 2 shows health benefits and net intervention costs. Based on efficacy results from the two trial settings, the IPTi intervention resulted in 223 and 89 prevented episodes of malaria in Ifakara and in Manhiça, respectively, for every 1000 immunized infants. Assuming a case-fatality rate of 1.57%, the number of deaths averted per 1000 infants receiving the intervention was estimated at 3.5 in Ifakara and 1.4 in Manhiça. The number of DALYs averted was estimated

at 118.9 per 1000 infants in Ifakara and 47.6 per 1000 infants in Manhiça. Intervention costs were estimated at US\$ 422 per 1000 immunized infants in Manhiça and US\$ 350 in Ifakara.

Cost-effectiveness ratios are presented in Table 3. Using efficacy data from the two trial sites, the costs estimated were as follows: per DALY averted, US\$ 3.7 (range: 1.6–12.2) for Ifakara and US\$ 11.2 (range: 3.6–92.0) for Manhiça; per malaria episode averted, US\$ 1.6 (range: 0.8–4.0) for Ifakara and US\$ 4.7 (range: 1.7–30.3) for Manhiça; and per death averted, US\$ 100.2 (range: 43.0–330.9) for Ifakara and US\$ 301.1 (range: 95.6–2498.4) for Manhiça.

Table 3 also presents cost-effectiveness ratios using an efficacy rate of 30% from the pooled analysis including the six IPTi trials with SP.³⁴ The costs estimated were as follows: per DALY averted, US\$ 7.9 (range: 3.2–27.0) for Ifakara and US\$ 8.3 (range: 3.3–27.5) for Manhiça; per malaria episode averted, US\$ 3.3 (range: 1.4–10.3) for Ifakara and US\$ 3.5 (range: 1.6–11.0) for Manhiça; per death averted,

Table 2. **Intervention costs, intervention efficacy and health benefits per 1000 infants receiving IPTi against malaria in Mozambique (Manhiça) and the United Republic of Tanzania (Ifakara), 2006**

Intervention effects	Ifakara	Manhiça
Intervention costs (US\$) ^a	350	422
IPTi efficacy (% and 95% CI) ^{a,b}	63.2 (44.2–74.6)	22.2 (3.9–37.0)
Malaria episodes averted	222.7	89.2
DALYs averted	118.9	47.6
Malaria deaths averted	3.5	1.4

CI, confidence interval; DALY, disability-adjusted life year; IPTi, intermittent preventive treatment in infants.

^a Sources: Intervention costs, ref. 44; IPTi efficacy, ref. 34.

^b Percentage reduction in malaria episodes.

US\$ 211.0 (range: 84.5–730.2) for Ifakara and US\$ 222.8 (range: 88.6–747.1) for Manhica.

Discussion

According to the cost-effectiveness analysis of IPTi, this strategy could be classified as highly cost-effective for controlling malaria in African infants.

The cost per DALY averted was under US\$ 12, and the cost per death averted was under US\$ 310 in both study sites. Due to the higher efficacy reported in the Ifakara trial, cost-effectiveness ratios were more favourable in that study than in the one conducted in Manhica. However, the reverse results were obtained when the pooled efficacy results were used.

IPTi offers an excellent value for the money when judged by a standard of under US\$ 50 per DALY averted for a “very cost-effective intervention”.²²

There are two further benefits of the IPTi intervention that are not reflected in these findings: anaemia prevention and cost savings. In past trials, the IPTi intervention (using SP) has been shown to reduce the incidence of anaemia by as much as 15.1% (95% CI: 6.3–23.1)³⁴. Furthermore, the fewer the cases of malaria, the less treatment-seeking and the greater the cost savings, a fact not reflected in the cost-effectiveness ratios presented above. While care is not sought for all malaria cases, most receive some form of therapy, either in a public or private clinic, a traditional

Table 3. Cost-effectiveness of malaria IPTi in a study in Mozambique (Manhica) and the United Republic of Tanzania (Ifakara), 2006

	Cost-effectiveness ratios ^a and ranges from Monte-Carlo simulation	
	Ifakara	Manhica
Using individual efficacy results		
Cost per DALY averted	3.7 (1.6–12.2)	11.2 (3.6–92.0)
Cost per malaria episode averted	1.6 (0.8–4.0)	4.7 (1.7–30.3)
Cost per malaria death averted	100.2 (43.0–330.9)	301.1 (95.6–2498.4)
Using pooled efficacy results		
Cost per DALY averted	7.9 (3.2–27.0)	8.3 (3.3–27.5)
Cost per malaria episode averted	3.3 (1.4–10.3)	3.5 (1.6–11.0)
Cost per malaria death averted	211.0 (84.5–730.2)	222.8 (88.6–747.1)

DALY, disability-adjusted life year; IPTi, intermittent preventive treatment in infants.

^a Ratios represent the estimated aggregate effect of the IPTi intervention divided by the estimated aggregate cost (US\$) of providing the intervention for a reference target population of 1000 immunized infants. The cost portion of the cost-effectiveness ratio includes only intervention costs; cost savings from fewer malaria cases are excluded.

care setting, or as self-treatment. These additional cost savings to the health system make the intervention even more attractive for ministries of health of malaria-endemic countries. When savings to the patient are considered (in health-care costs, transportation costs, travel time and time spent ill, etc.), the intervention becomes more attractive for its beneficiaries as well.

This study is beset by several uncertainties. The multivariate sensitivity analysis yielded wide confidence intervals resulting from the ranges of four key input parameters. For example, the cost per DALY averted ranged from

US\$ 1.6 to US\$ 12.2 in the United Republic of Tanzania and from US\$ 3.6 to US\$ 92.0 in Mozambique. However, these wide ranges were generated because a considerable degree of uncertainty in the selected parameters was allowed for, as shown in Table 4. Furthermore, even with an upper confidence limit of US\$ 12.2 per DALY averted in the United Republic of Tanzania and an upper confidence limit of US\$ 92.0 per DALY averted in Mozambique, IPTi is still an attractive health intervention. Counting only the financial cost of the IPTi intervention in Mozambique would reduce the upper confidence limit for the cost per DALY averted to US\$ 61.

A key uncertain variable – the case-fatality rate among infants – accounts for a significant share of the DALYs averted associated with malaria control interventions. For the multivariate analysis, a lower case-fatality rate of 1% was assumed. If the case-fatality rate were in fact zero, the cost per DALY averted would be considerably higher at US\$ 157.3 in the United Republic of Tanzania and US\$ 472.7 in Mozambique. However, excluding such a potential health benefit from the cost-effectiveness calculation would underestimate the cost-effectiveness of the IPTi intervention, since in Africa malaria causes a considerable number of deaths in the target population of children less than 2 years of age. Furthermore, if mortality impact were excluded from this analysis, it would also need to be excluded from the evaluation

Table 4. Distribution of probability parameters in probabilistic sensitivity analysis from study of malaria IPTi, Mozambique (Manhica) and the United Republic of Tanzania (Ifakara), 2006

Probability input variable	Type of probability distribution	Low estimate	Best estimate	High estimate	Source
IPTi efficacy					
Manhica	Triangular	0.039	0.22	0.370	16
Ifakara	Triangular	0.442	0.632	0.746	18
Pooled	Triangular	0.197	0.300	0.390	34
Case fatality rate	Triangular	0.010	0.0157	0.030	36,37
Malaria attack rate					
Manhica	Triangular	0.202	0.400	0.599	16
Ifakara	Triangular	0.182	0.353	0.528	18
Intervention costs per dose of SP (US\$)					
Manhica	Triangular	0.1065	0.1522	0.1979	44
Ifakara	Triangular	0.0898	0.1283	0.1668	44

IPTi, intermittent preventive treatment in infants; SP, sulfadoxine-pyrimethamine.

of other malaria control interventions (see below).

Compared with other malaria control interventions targeting young children in Africa, IPTi appears to be among the most cost-effective. For example, a previous study reported a cost of US\$ 10.3 per DALY averted for SP delivered weekly to infants between 2 and 12 months of age.³⁶ A recent African continent-wide cost-effectiveness analysis using secondary data sources reported the following costs per DALY averted: case management with artemisinin-based combination therapy, US\$ 10–12; insecticide-treated nets, US\$ 29–40; and indoor residual spraying, US\$ 32–41.⁴⁵ In a review of malaria prevention strategies in childhood, the cost per DALY averted using insecticide-treated nets was found to be above US\$ 9, including cost savings.²³ Thus IPTi, at a cost of less than US\$ 12 per DALY averted and with the likelihood of additional cost savings to the health system and patient, is found to be at least as cost-effective as other options for malaria control among infants.

From the health and cost-benefit points of view, IPTi merits serious consideration by health policy-makers, as it can have a major health impact in a vulnerable population, irrespective of the mortality impact of the intervention. Even if only the IPTi intervention costs are considered and potential cost

savings are excluded, cost-effectiveness ratios are highly favourable and good value for money.

The Intermittent Preventive Treatment in Infants Consortium identified several issues, in addition to safety, efficacy and potential interactions between IPTi and EPI vaccines, which have been included in a portfolio of research to evaluate the potential of incorporating IPTi into malaria control strategies. Acceptability, immunological effects and impact on drug resistance are currently being investigated, although published models provide reassurance that IPTi is unlikely to have a dramatic effect on the spread of drug resistance.^{46,47}

The difference between IPTi and intermittent preventive therapy in pregnancy (IPTp) should be understood by policy-makers, as these interventions do not directly compete with each other. While IPTi targets infants mainly to reduce malaria and anaemia among them, IPTp targets both mothers and infants and entails a broader set of health benefits for the infant, among them improved birth weight and fetal development, which result in significant long-term developmental gains. Hence, these strategies should, if possible, be implemented in parallel to attain optimal health benefits in these vulnerable populations.

In conclusion, the cost-effectiveness ratios of IPTi with SP are highly favour-

able in the two settings included in this study. These findings are likely to hold for other settings where IPTi is implemented provided a single-drug regimen is used for IPTi through the routine EPI schedule and malaria attack rates, IPTi efficacy rates and intervention costs resemble those evaluated in this study. Based on the cost-effectiveness of the intervention, it is recommended that IPTi with SP be implemented in malaria-endemic countries in sub-Saharan Africa as soon as possible, while ensuring that the intervention reaches the maximum number of infants through a routine contact point in the health system.

Acknowledgements

We are grateful to the members of the Intermittent Preventive Treatment in Infants Consortium for their input to this study and review of the paper. In particular we thank Andrea Egan and Elisa Sicuri (Barcelona Centre for International Health Research, Hospital Clinic, University of Barcelona, Spain) and Lesong Conteh (Swiss Tropical Institute, Basel, Switzerland). The authors thank the Bill and Melinda Gates Foundation for their funding to support the work of the IPTi Cost-Effectiveness Working Group.

Competing interests: None declared.

Résumé

Rapport coût/efficacité du traitement préventif intermittent contre le paludisme (TPI) chez le nourrisson au Mozambique et en République unie de Tanzanie

Objectif Estimer le rapport coût/efficacité d'un traitement préventif intermittent contre le paludisme (TPI) à base de sulfadoxine-pyriméthamine (SP) chez le nourrisson.

Méthodes Dans le cadre de deux essais antérieurs du TPI menés à Ifakara (République unie de Tanzanie) et à Manhiça (Mozambique), de la SP a été administrée à trois reprises à des nourrissons avant qu'ils atteignent 9 mois, par le biais du Programme élargi de vaccination. À partir des résultats d'efficacité de l'intervention et de l'incidence du paludisme dans la population cible, on a établi une estimation du nombre d'épisodes de paludisme clinique évités. On a utilisé à son tour ce nombre et un taux de létalité supposé de 1,57 % pour estimer le nombre d'années de vie corrigées de l'incapacité (DALY) et le nombre de décès évités. Sur la base de ces chiffres, on a ensuite évalué le coût de l'intervention (y compris les coûts de lancement et les coûts récurrents).

Résultats Le coût par épisode de paludisme clinique évité se montait à US \$ 1,57 (plage de variation : US \$ 0,8–4,0) à Ifakara et à US \$ 4,73 (plage de variation : US \$ 1,7–30,3) à Manhiça ; le coût par DALY évitée était de US \$ 3,7 (plage de variation : US \$ 1,6–12,2) à Ifakara et de US \$ 11,2 (plage de variation : US \$ 3,6–92,0) à Manhiça ; et le coût par décès évité atteignait US \$ 100,2 (plage de variation : US \$ 43,0–330,9) à Ifakara et US \$ 301,1 (plage de variation : US \$ 95,6–2498,4) à Manhiça.

Conclusion Du point de vue du système de santé et de la société, on s'attend à ce qu'un TPI à base de SP apporte des améliorations sur le plan sanitaire avec un bon rapport coût/efficacité. Dans une perspective économique, ce traitement offre un bon retour sur investissement pour les programmes de santé publique.

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