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Artemisinin-based combination therapy reduces expenditure on malaria treatment in KwaZulu Natal, South Africa

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Summary

INTRODUCTION There is growing international evidence that artemisinin-based combination therapy (ACT) is one of the few effective measures available to 'Roll Back Malaria'. However, concerns about the costs and affordability of ACT are obstacles to its widespread implementation. This paper explores some economic aspects of the implementation of artemether–lumefantrine (AL) to replace sulphadoxine–pyrimethamine (SP) in the KwaZulu Natal (KZN) province, South Africa.

METHODS Recurrent and capital costs for malaria treatment were compared at baseline and post-intervention for nine clinics and a sentinel rural district hospital. Changes in the unit costs of, and total expenditure on, malaria services were calculated and the cost effectiveness of AL relative to SP was assessed.

RESULTS The number of outpatient malaria cases and inpatient admissions both declined by 94% between 2000 and 2002. After accounting for the role of concurrent improvements in vector control, it was conservatively estimated that 36% of the decline in outpatient cases and 46% for inpatient admissions was attributable to changing the first-line drug to AL. Although AL is considerably more expensive than SP, its improved cure rate and reduced malaria transmission resulted in an estimated US$ 201 065 cost saving in 2002 alone for the subdistrict studied.

DISCUSSION In the context of effective vector control and low efficacy of existing monotherapy, ACT can reduce total expenditure on malaria services. However, the relevance of these findings requires careful consideration in countries with currently effective treatment policies and higher intensity malaria transmission.

keywords falciparum malaria, artemisinin-based combination therapy, economic evaluation, South Africa, costs

Introduction

Malaria-related morbidity and mortality has been increasing in Sub-Saharan Africa, primarily as a result of increased resistance to the commonly used first-line treatments, chloroquine and sulphadoxine–pyrimethamine (SP) (Trape *et al.* 1998; Snow *et al.* 2001). Artemisinin-based combination therapy (ACT) has been shown to improve cure rates, decrease malaria transmission and decrease antimalarial resistance on the north-west border of Thailand (Nosten *et al.* 2000). Improved cure rates and decreased gametocyte carriage have been confirmed in clinical trials in Africa (von Seidlein *et al.* 2000; International Artemisinin Study Group 2004). There is growing international consensus that wide-scale, systematic implementation of ACT is one of few effective measures that will enable malaria-endemic countries to achieve the ambitious goals set in Abuja in 2000 to 'Roll Back Malaria', particularly that of halving malaria morbidity and mortality by 2010. The World Health Organisation (WHO) explicitly recommended 'the use of ACT' in order to 'provide effective treatment against malaria and to slow the spread of drug resistance' in a statement released on 20 February 2002.

The South East African Combination Antimalarial Therapy (SEACAT) evaluation was initiated to establish whether or not the introduction of ACT as first-line treatment in the public sector in South Africa, Swaziland and southern Mozambique, improves cure rates, decreases malaria transmission, decreases antimalarial resistance and is cost-effective. Despite ACT's ability to improve malaria health outcomes, its cost and affordability continue to be a key area for policy debate for countries considering their use, particularly those in Sub-Saharan Africa. This paper evaluates the costs and cost effectiveness of ACT in the South African context, based on SEACAT evaluation findings from KwaZulu Natal (KZN) province, which was the first Ministry of Health in Africa to implement an ACT malaria treatment policy.

Malaria transmission in South Africa has been restricted to the north-eastern border areas with Mozambique and

Zimbabwe through the provision of prompt, effective treatment and vector control with widespread indoor residual spraying (IRS) since 1958. The intensity of malaria transmission in KZN is low, with an Annual Entomological Inoculation Rate of <1 (i.e. the probability of an infectious mosquito bite is less than once per person per year). Transmission is seasonal, mainly occurring between January and May, and *Plasmodium falciparum* accounts for the majority of infections.

Malaria treatment in South Africa is initiated on the basis of a positive malaria smear or rapid immunodiagnostic card test. In KZN province, SP replaced chloroquine as first-line treatment of uncomplicated malaria in 1988. Notifications of confirmed malaria cases increased dramatically from 1996 onwards, reaching epidemic levels in 1999 and 2000. Following 12 years of SP use in KZN, the therapeutic efficacy of SP (based on an *in vivo* study with 42 day follow-up) was only 12% by 2000 (Bredenkamp *et al.* 2001). The high treatment failure rate of SP (88%), increased vector resistance to pyrethroid insecticides and the reinvasion of the highly anthropophilic *Anopholes funestus* vector are considered to be the most important contributors to the 1999–2000 malaria epidemic (Hargreaves *et al.* 2000).

There has been a dramatic decline in malaria incidence in KZN since 2000, attributable to three interventions that were implemented in response to the malaria epidemic (Figure 1). First, the KZN Department of Health addressed vector resistance by re-introducing DDT to replace pyrethroids for IRS of traditional (but not Western style) homesteads in March 2000. Secondly, a regional collaboration implemented a community-based IRS programme in neighbouring southern Mozambique in October 2000. Finally, in response to high levels of SP treatment failure, first-line treatment of uncomplicated malaria was changed to an ACT, artemether–lumefantrine (AL), in January 2001. Quinine remains the recommended treatment for severe malaria, and uncomplicated malaria in pregnant women and infants under 1 year of age.

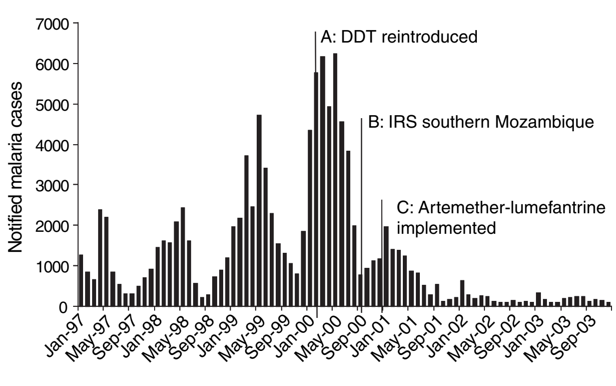

Figure 1 Number of notified malaria cases in KwaZulu-Natal by month in relation to timing of significant malaria control interventions. Source: South African National Department of Health Notification Data.

This paper presents the results of an economic evaluation of the change of first-line treatment of malaria in KZN from SP to AL, in terms of changes in health outcomes and costs of malaria services. On the basis of these results, the paper discusses policy issues related to cost and affordability of ACT in South Africa and other Sub-Saharan African countries.

Methods

Costing was undertaken from the provider's perspective; households incur minimal treatment seeking costs for malaria in South Africa. This was confirmed in a survey of 439 households in the district where the economic evaluation was conducted. It was found that 93% of those reporting a recent case of malaria had been treated for no charge at a public sector facility. The majority had walked to the facility and thus had not incurred transport costs. Changes in costs and health outcomes were measured between 2000 (baseline) and 2002 (post-intervention). Cost and health outcome data were retrospectively collected from a sample of public sector health care facilities within the Ingwavuma district. This district, which has the highest intensity malaria transmission in KZN, has two district hospitals, each with a number of satellite clinics. One of these hospitals (Manguzi) and its nine fixed satellite clinics were included in this study.

Both annual recurrent and capital costs (replacement cost of buildings, furniture, equipment and vehicles, annualized at 8% over their estimated useful life) of providing outpatient and inpatient malaria services were calculated. The annualization rate was set at the long-term government bond rate in South Africa, which is generally accepted practice in economic evaluations. The proportion of total facility recurrent costs (excluding drug and diagnostic test costs) and annual capital costs attributable to malaria patients was based on malaria patients as a percentage of total facility patients. Costs of antimalarials and diagnostic tests were calculated separately, based on information from facility records on price and quantities of antimalarials and rapid tests consumed (dispensed plus wastage) for a given year of analysis. All baseline data were inflated to 2002 prices, and all cost data are expressed in US$ using the average exchange rate in 2002 of US$1 = ZAR 10.5.

Although the concurrent implementation of effective IRS and antimalarial treatment policy has undoubtedly benefited public health, it precludes precisely quantifying the individual impact of each of these interventions. No data are currently available on the relative impact of IRS or of ACT as individual interventions on malaria morbidity and mortality in the South African context. Given this, we chose to conduct a Delphi survey in an attempt to reach consensus on the approximate percentage contribution of different 'interventions' to the decline in malaria cases, admissions and deaths. A Delphi survey is useful when the only available alternative is relying on anecdotal or subjective assessments (Broomfield & Humphries 2001). The Delphi technique is a structured approach to eliciting expert opinion and reaching consensus among these experts (Gupta & Clarke 1996). It involves an initial round of answers to a questionnaire, with controlled feedback to participants in an anonymous format in a second round. A number of iterations occur until consensus is reached.

In the first round of the Delphi survey, a questionnaire was electronically sent to a group of 10 international malaria experts requesting them to provide estimates of the percentage contribution of each intervention. The key interventions, as indicated in Figure 1, were the reintroduction of IRS with DDT in KZN, the introduction of IRS in southern Mozambique and the implementation of AL as the first-line treatment for outpatient malaria cases.

In response to an open question regarding other factors potentially contributing to the change in the number of malaria cases in KZN, Delphi panellists also identified climatic change as a possible but less influential contributor. In the second round of the survey, summaries of the first round estimates were provided to assist panellists in revising their first round estimates. Nine, eight and seven panellists responded in rounds 1, 2 and 3 respectively, the final seven having responded in all rounds. The estimates obtained from round 3 have been used in this analysis.

This paper is concerned with the evaluation of only one intervention, namely the change of treatment policy to AL. The estimated contribution of the introduction of AL to the decline in malaria cases, admissions and deaths is 36%, 46% and 62% respectively, based on the medians from the Delphi survey. Sensitivity analyses were conducted using the Delphi estimate ranges (lower and upper percentage contributions).

The incremental cost effectiveness of the change from SP monotherapy (baseline) to AL therapy (post-intervention) has been evaluated, with effectiveness being calculated as the malaria deaths averted. A decision tree (Figure 2) was used in this analysis. One-way and multi-way sensitivity

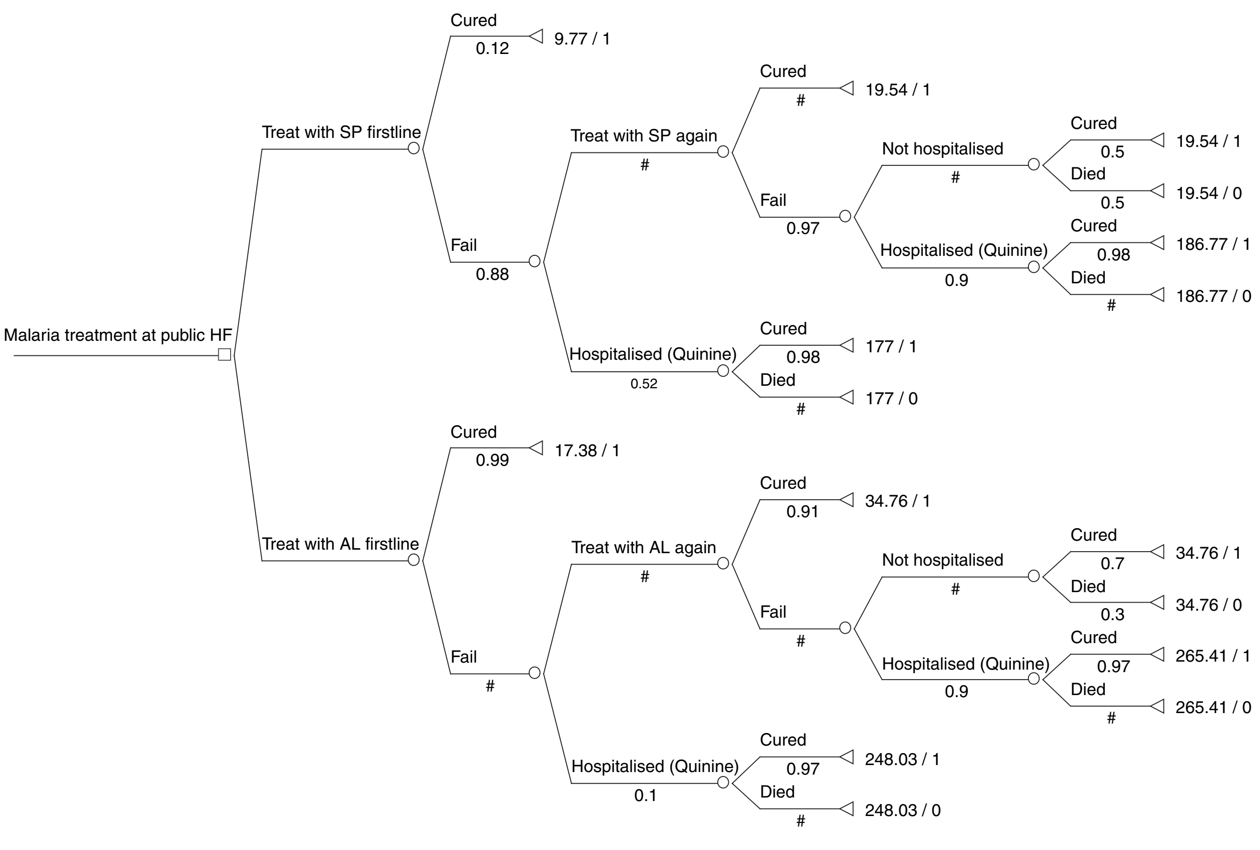

Figure 2 Decision tree comparing SP and AL as first-line treatment options.

analyses were conducted to explore the impact of changes in estimates for variables where data were subject to possible variation, including:

- The percentage contribution of ACT to the decline in malaria cases, admissions and deaths using the range of Delphi estimates;
- The annualization rate used for capital expenditure, given that some studies use lower rates than the 8% suggested in this study;
- The length of stay of hospitalized malaria patients, given that the hospital studied (Manguzi) has an average length of stay of 7 days while some others report an average length of stay of 3 days per malaria admission;
- The impact if the price of SP had been equivalent to the international median price, instead of the inflated price actually paid by KZN health authorities.

Results

Changes in malaria health outcomes

There was a decline of 94% in annual malaria outpatient cases from 23 186 at baseline (2000) to 1312 after the intervention(s) (2002) and a 94% reduction in malaria admissions from 1902 to 108 over the same 2-year period in the sample of facilities in the Manguzi subdistrict (see Figure 3). This has been accompanied by an overall reduction in general hospital outpatient visits (5%), general admissions (19%) as well as inpatient days (9%) at hospital level, but not at clinic level. A greater decline in overall hospital outpatient visits and admissions following the marked decline in malaria cases and admissions was prevented by the increasing burden at health facilities of the HIV/AIDS epidemic in KZN.

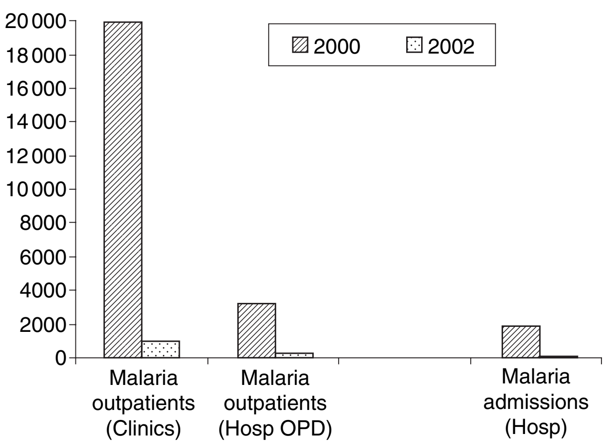

Figure 3 Changes in Malaria cases and admissions between 2000 and 2002 (Manguzi subdistrict). Source: Statistics Department, Manguzi Hospital (Ingwavuma, KZN).

Malaria treatment costs

Summaries of baseline and post-intervention treatment costs for malaria outpatients and inpatients are presented in Tables 1 and 2 respectively. There were substantive declines in expenditure on outpatient malaria services between the baseline and post-intervention periods, at both clinic and hospital levels, resulting in considerable cost savings (Table 1). This is attributable to the substantive decline in malaria outpatient cases. Table 1 also shows a decline in expenditure on antimalarials, despite the higher unit price of AL compared with SP (US$3.24 and 1.65 respectively for an adult dose* at 2002 prices). Despite the marked reduction in malaria cases, expenditure on malaria diagnostics has not decreased by the same proportion because malaria still needs to be excluded in febrile patients, although only a small proportion (8% in 2002) tested positive. The outpatient unit cost at the hospital is more than twice as high as that at clinics, mainly due to higher personnel and capital unit costs at hospital level.

When clinic and hospital data are combined, the total baseline outpatient malaria cost was US$226 464 for 23 186 malaria patients, resulting in an average cost per malaria outpatient visit of US$9.77. Total outpatient costs post-intervention were US$22 809 for 1312 malaria patients, translating into an average cost per malaria outpatient visit of US$17.38.

Table 2 shows that there has also been a substantive decline in expenditure on malaria inpatient activities, resulting in further cost savings. It is important to note that malaria management for inpatients has not changed since 2000, i.e. they still receive quinine for 7 days, hence these cost savings are solely attributable to the massive reduction in number of malaria admissions.

Evaluation of AL intervention in KZN

It was important to attempt to separate out the contribution of the introduction of an effective ACT (AL) alone, relative to other malaria control interventions during this

* South Africa generally procures drugs at prices significantly higher than international median prices. The price at which KZN procured SP in 2000 (more than 20 times higher than the international median price) has been used in our analyses and has been inflated to 2002 prices. A sensitivity analysis uses the international median price.

Table 1 Economic costs of treatment (SP *vs.* AL) for outpatient malaria cases in Manguzi subdistrict, KwaZulu Natal province (2002 US$)

	Clinics (9) baseline	Clinics (9) post-intervention	% Reduction	Hospital baseline	Hospital post-intervention	% Reduction
Antimalarial costs	27 794	1694	93.9	4429	120	97.3
Cost of malaria tests	23 312	7288	68.7	6566	3583	45.4
Other recurrent expenditure*	85 776	4302	95.0	62 424	4976	92.0
Capital expenditure	12 982	552	95.7	3182	295	90.7
Total malaria expenditure	149 864	13 836	90.8	76 600	8973	88.3
Cost per malaria outpatient	7.52	13.50		23.49	31.26	
Cost savings		136 028			67 628	

*Other recurrent expenditure refers to annual expenditure on personnel (accounting for 50–70% of this expenditure category), consumables, maintenance, utilities, administration and expenditure on other recurrent items.

Table 2 Economic costs of malaria inpatients in Manguzi Hospital (2002 US$)

	Hospital baseline	Hospital post-intervention	% Reduction
Antimalarial costs	14 828	799	94.6
Cost of malaria tests	3823	1345	64.8
Other recurrent expenditure	272 011	21 062	92.3
Capital expenditure	39 351	2451	93.8
Total malaria costs	330 013	25 658	92.2
Average cost per malaria inpatient-day (US$)	24.8	33.9	−36.9
Average cost per malaria admission (US$)	173.5	237.6	−36.9
Cost savings		304 356	

period, to these changes in hospital and clinic level malaria expenditure. The Delphi survey indicated that the two interventions considered the most important contributory factors to the reduction in malaria cases, admissions and deaths in KZN between 2000 and 2002 were the change of first-line treatment policy and re-introduction of IRS with DDT. Improved vector control through community-based IRS in neighbouring southern Mozambique was considered the third most important contributor to decreased malaria morbidity in KZN. The results from the Delphi survey attributed a median contribution of 36% (range: 25–50%) and 46% (range: 35–60%) to the decline in malaria cases and malaria admissions respectively, to ACT implementation alone. This implies that if the ACT (AL) policy change is the only intervention implemented, baseline malaria cases and admissions would have declined by about 36% and 46% respectively by 2002.

Details of the total costs, unit costs and cost saving associated with the change to AL, based on the median Delphi estimates, compared with an assumption of 100% of the observed changes in malaria cases and admissions being attributable to this intervention, are presented in Table 3. In addition, a sensitivity analysis using the ranges of the Delphi estimates shows that changing first-line treatment from SP to AL alone resulted in reduced malaria cases and admissions as well as cost savings, even when the most conservative estimates of changes in health outcomes (25% and 35% for outpatients and inpatients respectively) are used.

A further sensitivity analysis indicated that if KZN had paid a substantially lower price for SP (i.e. the international median price[†]), the cost savings would have been lower, but would not have been lost. For example, total cost savings for outpatient malaria services would have been US$176 198 instead of US$203 656, and would have been US$71 751 instead of US$99 209, if 100% and 25% respectively of the decrease in outpatient numbers were assumed to be attributable to the introduction of AL.

Multi-way sensitivity analyses indicate that these key findings remain unaltered when the value of variables, around which there is some uncertainty, change (Table 4). The unit cost estimates change very little and although there is a relatively broad range in the value of estimated cost savings, none of the sensitivity analyses change the finding that the introduction of AL as the first-line malaria treatment in KZN has achieved substantial cost savings.

A comparison of the costs and effectiveness of SP *vs.* AL as the first-line treatment, using a decision tree model, shows that the average cost per life saved is US$18 with AL compared with US$158 with SP. Thus, in the KZN context, AL is a more cost-effective first-line treatment than SP. Sensitivity analyses performed on the decision tree

[†] The International Median Price was obtained from the Management Sciences for Health International Drug Price Indicator Guide website (http://erc.msh.org/dmpguide/). The median price of SP across suppliers cited in the Guide in 2000 was inflated by 15% for insurance and transport, as recommended by MSH.

Table 3 Evaluating the impact of a new drug (AL) alone (based on Manguzi subdistrict sample)

	Total Cost (2002 US$)	Outpatients/inpatient-days	Unit cost (2002 US$)	
Baseline [treated with SP for outpatients and with quinine (7 days) for inpatients]				
Malaria outpatient services	226 464	23 186	9.77	
Malaria inpatient services	330 013	13 314	24.79	
Sensitivity analysis	**Malaria outpatient cost**	**No. of outpatient visits**	**Average cost per malaria outpatient**	**Cost savings (2002 US$)**
Post-intervention [treated with AL for outpatients and with quinine (7 days) for inpatients]				
Malaria outpatients (100% change)	22 808	1312	17.38	203 656
Adjusted for 36% (median)	110 664	15 311	7.23	115 801
Adjusted for 25% (lower range)	127 256	17 718	7.18	99 209
Adjusted for 50% (upper range)	89 546	12 249	7.31	136 918
Sensitivity analysis	**Malaria inpatient cost**	**No. of inpatient days**	**Average cost per malaria inpatient-day**	**Cost savings (2002 US$)**
Malaria inpatient-days (100% change)	25 658	756	33.94	304 356
Adjusted for 46% (median)	244 750	7537	32.47	85 264
Adjusted for 35% (lower range)	289 359	8919	32.44	40 654
Adjusted for 60% (upper range)	187 974	5779	32.53	142 039

Table 4 Multi-way sensitivity analysis results (annualization rates; average length of inpatient stay and contribution of AL to decline in malaria cases and admissions)

	Lowest estimates	Highest estimates
Cost per malaria outpatient	US $7.05	US $7.31
Variable assumptions	3% annualization rate for capital 25% contribution of AL to decline in malaria cases	8% annualization rate for capital 50% contribution of AL to decline in malaria cases
Cost saving on outpatient care	US $99 209	US $136 918
Variable assumptions	8% annualization rate for capital 25% contribution of AL to decline in malaria cases	8% annualization rate for capital 50% contribution of AL to decline in malaria cases
Inpatient unit cost	US $31.44	US $34.44
Variable assumptions	3% annualization rate for capital 35% contribution of AL to decline in malaria admissions 7 days average length of stay	8% annualization rate for capital 60% contribution of AL to decline in malaria admissions 3 days average length of stay
Cost saving on inpatient care	US $40 654	US $244 693
Variable assumptions	8% annualization rate for capital 35% contribution of AL to decline in malaria admissions 7 days average length of stay	8% annualization rate for capital 60% contribution of AL to decline in malaria admissions 3 days average length of stay

model did not alter the finding of relative cost effectiveness of AL over SP.

Discussion

Early results of the public health impact of AL implementation in KZN, which has a relatively well-developed rural primary health care infrastructure, and effective vector control measures, are most encouraging. While it is difficult to separate out the individual impact of these interventions, Figure 1 highlights that IRS is a critical component of the KZN malaria control programme and that the reintroduction of DDT is considered to have contributed substantially to the recent decline in malaria in this province. The established use of definitive diagnostic rapid tests, limiting the unnecessary use of antimalarials, is another important component of the malaria control programme in KZN.

This evaluation shows that the AL treatment policy is not only more cost-effective than SP monotherapy, but that it has also resulted in substantial cost savings in the KZN context. This finding holds even if the most conservative estimates of the relative contribution of the change in drug regimen are used, and if the highly inflated SP prices paid by KZN are replaced with international median prices. These cost savings resulted primarily from the decrease in the total number of malaria cases and the number of malaria hospital admissions. Although this study was undertaken in the district with the highest intensity transmission, the results are likely to be robust in relation to other lower intensity transmission districts. This is based on the fact that the 94% decline in the number of malaria cases in the Manguzi subdistrict between 2000 and 2002 is comparable with the decline in the number of notified malaria cases in KZN as a whole over this same period (also 94%; Figure 1). Our findings are consistent with the improved cure rates and decreased malaria transmission associated with the widespread use of ACT in north-west Thailand, where malaria transmission patterns are similar to those in KZN. A 47% decline in malaria cases was observed within 1 year of the introduction of ACT (artesunate plus mefloquine) in north-west Thailand, which increased to a sixfold reduction over 10 years (Price *et al.* 1996; Nosten *et al.* 2000).

The costs of the policy change itself have not been quantified here, as these were not substantial within the KZN context. These costs were limited to policy change consensus-building activities, printing new treatment guidelines and workshops to train health care providers. In other African countries these have been predicted to be far higher. In Tanzania, for example, the non-drug costs of ACT implementation over 5 years are predicted to be US$13.79 million (J. Mulligan, personal communication). The remarkably low costs of policy change in KZN relate to the limited distribution of malaria transmission, the established national Malaria Advisory Group and the strong existing malaria control programme and pharmaceutical services in KZN, whose staff co-ordinated and facilitated the new first-line drug policy implementation process as part of their day-to-day activities.

There are a number of factors that may influence the relevance of the findings of this study to other African countries. For example, KZN has a relatively low malaria prevalence and intensity of transmission. The extent of potential cost savings is partly influenced by the use of a definitive (rather than clinical) diagnosis for malaria in KZN, which undoubtedly contributed to minimizing expenditure on ACT. Clinical diagnosis (particularly in countries with low to moderate malaria prevalence) is likely to increase overall expenditure on antimalarials when ACT is implemented as first-line treatment.

The short-term benefits of implementing ACT are likely to be greatest in areas where there are high levels of treatment failure of the current malaria treatment. Only a few studies in African countries have been published reporting levels of monotherapy treatment failure similar to those observed in KZN. However, there is concern that other countries carrying similar burdens underestimate resistance as they do not detect failures more than 14 days, after treatment, as this is the follow period recommended by the WHO for countries with intense malaria transmission (White 2002). As ACT also decreases transmission directly by decreasing gametocyte carriage, the effect of ACT on malaria morbidity in contexts where current monotherapy is effective, needs to be established.

The effect of ACT on delaying the emergence and spread of antimalarial resistance has not yet been established in Africa, although has been demonstrated in north-west Thailand (Nosten *et al.* 2000). If confirmed, this would provide further justification for the widespread use of ACT and would substantially increase the cost savings reported here.

Although the substantial cost savings in KZN are encouraging, these may not be widely generalizable. Changes in malaria treatment expenditure occurring when first-line treatment is changed, and the relative cost effectiveness of alternative malaria treatment policies, as well as the costs of policy change, need to be evaluated in countries where (i) the intensity of malaria transmission is higher, (ii) malaria is clinically and not definitively diagnosed, (iii) current monotherapy treatment policy is highly effective, and (iv) the primary health care infrastructure is less well developed and most malaria treatment is sought in the informal or private sectors.

Conclusions

Early results on the impact of malaria control policy changes in KZN emphasize the synergy between improved vector control and ensuring widespread use of ACT. The findings also highlight the greater effectiveness and significant cost savings associated with the implementation of AL. These cost savings result from the improved clinical cure rates and decrease in malaria transmission achieved with AL. The extent to which similar results can be achieved in other settings requires detailed consideration.

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References

Bredenkamp B, Sharp B, Mthembu S, Durrheim D & Barnes K (2001) Failure of sulfadoxine-pyrimethamine in treating *Plasmodium falciparum* malaria in KwaZulu-Natal. *South African Medical Journal* **91**, 970–972.

Broomfield D & Humphries GM (2001) Using the Delphi technique to identify the cancer education requirements of general practitioners. *Medical Education* **35**, 928–937.

Gupta UG & Clarke RE (1996) Theory and applications of the Delphi Technique: a bibliography (1974–1995). *Technological Forecasting and Social Change* **53**, 185–211.

Hargreaves K, Koekemoer L, Brooke B, Runt R, Mthembu J & Coetzee M (2000) *Anopholes funestus* resistant to pyrethroid insecticides in South Africa. *Medical and Veterinan Entomology* **14**, 181–189.

International Artemisinin Study Group (2004) Artesunate combinations for treatment of malaria: meta-analysis. *Lancet* **363**, 9–17.

Nosten F, van Vugt M, Price R *et al.* (2000) Effects of artesunate mefloquine combination on incidence of *Plasmodium falciparum* malaria and mefloquine resistance in Western Thailand: a prospective study. *Lancet* **356**, 297–302.

Price R, Nosten F, Luxemburger C *et al.* (1996) Effects of artemisinin derivatives on malaria transmissibility. *Lancet* **347**, 1654–1658.

von Seidlein L, Milligan P, Pinder M *et al.* (2000) Efficacy of artesunate plus pyrimethamine-sulfadoxine for uncomplicated malaria in Gambian children: a double blind, randomized, controlled trial. *Lancet* **355**, 352–357.

Snow W, Trape J & Marsh K (2001) The past, present and future of childhood malaria mortality in Africa. *Trends in Parasitology* **17**, 593–597.

Trape J, Pison G, Preziosi M *et al.* (1998) Impact of chloroquine resistance on malaria mortality. Comptes rendes de l'Academie des Sciences. *Sciences de la vie* Serie III **321**, 689–697.

White NJ (2002) The assessment of antimalarial drug efficacy. *Trends in Parasitology* **18**, 458–464.

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