# Will A Global Subsidy Of New Antimalarials Delay The Emergence Of Resistance And Save Lives?

A modeling exercise shows that even modest subsidies can have an impact.

**by Ramanan Laxminarayan, Mead Over, and David L. Smith**

**ABSTRACT:** Artemisinin-based combination treatments (ACTs) are seen as an important tool in the global effort to roll back malaria. With parasite resistance to chloroquine increasing rapidly in many parts of the world, there is greater recognition of the need for a globally coordinated strategy to ensure that artemisinins are not used as monotherapy, which has the potential to cut short their useful therapeutic life. We find that even a partial subsidy could delay the emergence of resistance and that a delay in implementing a subsidy for ACTs could facilitate the emergence of resistance and lower the economic value of ACTs. [*Health Affairs* 25, no. 2 (2006): 325–336; 10.1377/hlthaff.25.2.325]

T HE BOARD ON GLOBAL HEALTH of the Institute of Medicine (IOM) convened a committee in 2002 to examine the economics of alternative strategies to treat malaria, given the declining effectiveness of chloroquine and its successors in most malarious regions of the world. The IOM committee's task was to recommend a strategy that would both enable the widespread use of effective drugs to fight the disease and delay the emergence of resistance to artemisinin compounds for as long as possible. In its final report, *Saving Lives, Buying Time*, the committee noted important reasons for the immediate introduction of artemisinin-based combination treatments (ACTs)—notably, the need to minimize the use of artemisinin monotherapy (AMT), which could engender rapid resistance to this valuable class of drugs, and the need to reduce deaths due to ineffective antimalarial treatments.[1] Furthermore, the need for an internationally coordinated policy was identified, because the evolution of resistance to artemisinin derivatives as a result of poor treatment choices made in any single country could compromise the effectiveness of ACTs everywhere else. With these objec-

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tives in mind, the committee recommended the establishment of an international fund that would buy ACTs from producers at a dollar per dose and resell it to anyone at one-tenth of that price, thereby ensuring a stable demand for ACTs and scale economies that could ultimately bring down the price of these drugs.

During subsequent deliberations at the World Bank, concern was raised about this global subsidy, on the grounds that while subsidies for any drug (including ACTs) create substantial benefits for the individual patients who take the drug, they typically entail negative externalities by increasing selection for resistant pathogens—an international public "bad."[2] As the IOM committee itself had noted, "If ACTs become as inexpensive to consumers as chloroquine is now, chances are they will be used as frequently as chloroquine, including over-use for febrile illnesses due to causes other than malaria. All overuse increases the probability that artemisinin-resistant parasites will arise and spread."[3]

Therefore, the committee's recommendation to encourage (through a subsidy) greater use of ACTs would delay resistance only if the subsidized ACT crowded out AMT or partner drug monotherapy (PMT), which could lead to more rapid development of drug resistance.[4] More to the point, a global subsidy of ACTs would contribute to the expansion of a global public good—extended therapeutic life for artemisinins—only if the benefits of crowding out monotherapies outweighed the resistance-related costs of greater use of ACTs.[5]

Global subsidies are not the only mechanism to deal with drug resistance, however. Others have addressed the issue of public goods in the context of communicable disease control and have discussed other methods of dealing with global drug resistance.[6] Moreover, there were other reasons for subsidizing ACTs, as pointed out by the IOM committee. An up-front subsidy would ensure stable demand for ACTs, encourage suppliers to invest in scaled-up production, and lower the price. The centrally administered subsidy would lower the costs of standardizing, procuring, and distributing the drugs. Moreover, a subsidy would achieve other objectives, such as discouraging counterfeit antimalarial drugs and allowing low-income countries to choose ACTs as their first-line treatment without certain funding from donors. None of these arguments was specific to ACTs or even to malaria, for that matter. They could be made just as easily in favor of a global subsidy for ciprofloxacin to treat diarrheal disease or for anti-epileptic drugs. The global public goods–based argument for subsidizing ACTs is tied to the expectation that a low-cost provision of ACTs would discourage AMT and PMT use and would therefore delay the emergence of resistance to ACTs.

The central question motivating our study was whether the benefits of a global subsidy of ACTs to discourage the use of AMT and PMT were likely to outweigh the drawbacks of potentially faster development of resistance to ACTs because of their widespread use. Our primary objective was to explore whether and under what conditions—involving ACT use and the counterfactual of AMT and PMT use—a global subsidy for ACTs would prolong the useful therapeutic life of

artemisinin as an antimalarial. A broader issue we addressed was whether a global subsidy for ACTs would save lives and avert morbidity (compared with doing nothing) and, if so, at what cost. Underlying these objectives is the complex relationship between the development and spread of an artemisinin-resistant strain of *Plasmodium falciparum* and relative prices, availabilities, and substitution elasticities in consumption of ACTs and monotherapies.

## Study Methods

We addressed the question of the extent to which ACTs' effectiveness is a global public good, using a mathematical model of malaria transmission, resistance, immunity, and economics. The analysis compared the introduction of an ideal ACT subsidy with counterfactual scenarios in which AMT and PMT are used in a small proportion of patients, in the absence of ACTs. Critical parameters were the elasticities that characterize the response of consumer demand to the lower price of ACTs, both increasing their demand for ACTs and encouraging ACTs as a substitute for monotherapies. We explored reasonable ranges of cross-elasticities of demand between ACT and monotherapies.

We approached optimal policy for this analysis from the perspective of minimizing the incremental treatment costs per death averted. Input parameters for cost of illness and treatment were drawn from the existing literature and obtained from Médecins sans Frontières.[7] We restricted treatment costs to drug costs alone, because much of malaria treatment in sub-Saharan Africa occurs in the private sector through small shops and vendors. Including identical nondrug treatment costs to all treatment regimens diluted the importance of drug costs and did not change any of the results qualitatively. To provide information to donors on the likely value of a subsidy, we also used a perspective of including only the subsidy costs of ACTs.

We assumed the cost of extending treatment coverage to be linear in the number of patients treated; this might have had some bearing on our qualitative results. One alternative was to use a nonlinear function with decreasing marginal costs of coverage initially when coverage is small, and increasing marginal costs of coverage when all of the easily accessible patients have been reached and additional patients are more expensive to treat. However, there is little guidance in the malaria literature to guide a formulation of a cost function. We ran simulations for a ten-year planning horizon. For cost-effectiveness calculations, we discounted the streams of costs and health benefits at an annual rate of 3 percent.

Finally, the quality of ACT treatment, including the sensitivity and specificity of diagnosis, and treatment compliance are important considerations but outside the purview of this paper. Quality and compliance might vary because of differences in patients (such as education and household income), duration of treatment, side effects, rapidity with which a cure is effected, and other factors. However, there is little quantitative evidence on how compliance is influenced, and the

role of compliance in the evolution of resistance remains poorly understood.[8]

■ **Malaria model.** We developed an entomological-epidemiological model to model transmission of malaria and emergence and spread of single-drug and multi-drug resistance to antimalarials. Briefly, the model used was an extension of a simple, compartmental model of malaria transmission modified to include the evolution of resistance to an antimalarial encoded at a single locus.[9]

■ **Treatment demand.** The demand for ACTs to treat malaria depends on the efficacy of ACTs and their cost to patients. Other factors that might influence the decision to seek treatment include age, sex, geographical location, degree of malaria endemicity, proximity to a trained health care provider, and other sociocultural factors and are assumed to be the same for all treatments. The interaction of economic (behavioral) and epidemiological variables is self-evident. If ACTs are too expensive, they are less likely to be used and will have little impact on preventing malaria deaths or influencing the evolution of resistance. Also, the greater the intensity of malaria transmission, the faster and more lasting the immunity that is acquired, and for those individuals there will be a lower likelihood of symptomatic disease and less need to seek drug treatment later in life.[10]

Typically, only a fraction of patients infected with malaria parasites are symptomatic and likely to seek antimalarial treatment. We assumed this fraction to be 20 percent in our model.[11] Varying this parameter (10–30 percent) made no difference to our qualitative results. The demand for a specific antimalarial treatment is a function of the quality-adjusted price of other antimalarials that are available. The fraction of symptomatic malaria patients treated with antimalarial $X$ (AMT) can be represented as a function of the price of AMT (or price of $X$), price of PMT (or price of $Y$), and the price of the combination (or price of $XY$).

A subsidy that will lower the price of a combination ($XY$) to the patient has two effects. First, it leads to increased use of the antimalarial $XY$ (that is, ACT) according to the assumed demand schedule. Second, it encourages substitution away from monotherapies to the ACT combination $XY$. The net result will typically be to increase overall use of antimalarials. Although there are no data to support the magnitude of these shifts in antimalarial-use patterns in response to a subsidy to ACT, we used some plausible own- and cross-price elasticities.[12]

In general, useful operational research to support the implementation of a global ACT subsidy could be to estimate the demand for antimalarial therapy as a function of the perceived efficacy of therapy, price, and other factors.[13]

■ **Parameter values and scenarios considered.** Entomological and epidemiological parameter values considered are described in an online appendix and justified elsewhere.[14] We tested model sensitivity over a wide range of economic, epidemiological, and entomological parameters. We assumed the price of AMT to be one dollar per treatment course (three days) and the price of PMT to be thirty cents per treatment course. The price of ACT was $1.30 in the baseline (no-subsidy) case. All cost parameters were varied in the sensitivity analysis.

Exhibit 1 describes the assumed levels of treatment coverage for different levels of subsidy.[15] Under scenario A (no subsidy), 4 percent of all symptomatic cases of malaria are treated with AMT (drug $X$), 16 percent are treated with the partner drug $X$ as monotherapy, and 1 percent are treated with ACTs.

In scenario B, a partial subsidy (assumed to be eighty cents per dose) is provided to ACTs, which drops the cost to fifty cents per dose. As a consequence, under the baseline assumption on demand elasticity, the use of both AMT and PMT drops by almost a third, and 15.1 percent of symptomatic infections are treated with ACTs. Overall use of antimalarials increases from 21 percent of symptomatic infections in the no-subsidy case to 32 percent under the partial subsidy. These changes in usage correspond to an own-price elasticity of ACT of −1.97 and a cross-price elasticity with respect to AMT and PMT of 0.17.

With a broader subsidy program (scenario C), under which each dose of ACT is subsidized by a dollar (for a final price of thirty cents per treatment course), the use of ACTs increases to 43.8 percent and the use of compromising monotherapy drops to 2.2 percent for AMT and 8.9 percent for PMT. These levels correspond to an own-price elasticity of −1.53 for ACTs and a cross-price elasticity of 0.46.

In scenario D, there is a two-year delay in implementing a full subsidy program, during which time AMT and monotherapy with the partner drug Y continue at levels encountered in the no-subsidy scenario. We modeled this scenario using the same overall coverage response assumptions as in scenario A for the first two years and scenario C thereafter.

In scenario E, a partial subsidy is introduced for two types of ACTs (for example, artesunate + amodiaquine and artesunate + sulfadoxine-pyrimethamine). Overall use of ACTs and monotherapies is identical to that in scenario B. In sce-

**EXHIBIT 1**
**Treatment Coverage For Different Scenarios For Baseline Parameters, Global Antimalarial Treatments**

| Scenario | Artemisinin monotherapy (X) | Partner drug monotherapy (Y) | Partner drug monotherapy (Z) | ACT (XY) | ACT (XZ) | Self-treatment |
|---|---|---|---|---|---|---|
| A: no subsidy | 4.0% | 16.0% | –[a] | 1.0% | –[a] | 79.0% |
| B: partial subsidy (ACT with compromising monotherapy) | 3.4 | 13.7 | –[a] | 15.1 | –[a] | 67.8 |
| C: full subsidy (ACT now) | 2.2 | 8.9 | –[a] | 43.8 | –[a] | 45.1 |
| D: delayed subsidy; mono-therapy in years 1 and 2, full ACT subsidy starting in year 3) | 4.0 / 2.2 | 16.0 / 8.9 | –[a] / –[a] | 1.0 / 43.8 | –[a] / –[a] | 79.0 / 45.1 |
| E: partial subsidy for two ACTs | 3.4 | 6.9 | 6.9% | 7.5 | 7.5% | 67.8 |
| F: full subsidy for two ACTs | 2.2 | 4.4 | 4.4 | 22.6 | 22.6 | 43.8 |

**SOURCE:** Authors' calculations and analysis.
**NOTES:** See Appendix B for an explanation of the elasticity parameter, online at http://content.healthaffairs.org/cgi/content/full/25/2/325/DC1. ACT is artemisinin combination treatment.
[a] Not applicable.

nario F, a full subsidy is implemented for these two types of ACTs, and use of monotherapies is effectively discouraged, as in scenario C.

## Study Results

Under the no-subsidy scenario (A), the treatment failure rate rises rapidly but levels off after a short period (Exhibit 2). The treatment failure rate at equilibrium is lower because relatively few people receive treatment without a subsidy program. Treatment failures rise more quickly under the partial subsidy (scenario B) because resistance to the separate drugs emerges earlier when compromising monotherapies are used alongside ACTs. With the full subsidy (scenario C), the rise in the treatment failure rate is delayed because of lower use of compromising monotherapy, but it reaches equilibrium at a relatively higher rate because of the greater proportion of patients receiving treatment. Failure rates with delayed subsidy of ACTs (scenario D) show that this is likely to be the worst strategy. Failure rates rise early, following the same path as the no-subsidy case. The treatment failure rate drops at year 2 following the introduction of a full subsidy but climbs back quickly because of the higher frequency of resistance to the separate drugs that arose when artesunate and the partner drug were used as monotherapy.

In scenario E, the partial subsidy increases the use of two different ACTs, as described above. This strategy results in a slower increase in treatment failure rates compared with scenarios A–D. A full subsidy that covers two ACTs with unrelated partner drugs (scenario F) delays the emergence of resistance even more.

The treatment and subsidy costs for deaths averted in scenarios B–F are incremental to the baseline of no subsidy, because that is assumed to represent the status quo (Exhibit 3). Scenario A, with no subsidy, resulted in the most deaths over the ten-year horizon for the population of one million. The partial subsidy to ACTs of eighty cents per treatment course in scenario B lowered deaths by roughly 4 percent at a cost of roughly $1,230 per death averted. The predicted cost

**EXHIBIT 2**
**Time Paths Of Daily Treatment Failure Rates For Scenarios A–F Over Ten Years**
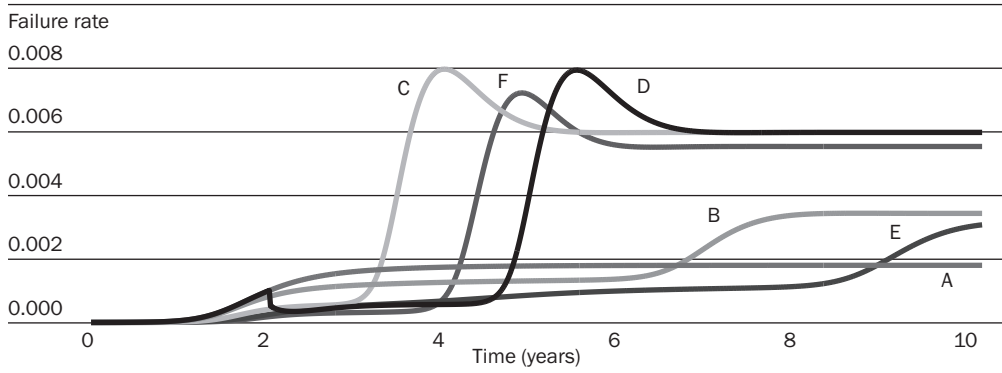


SOURCE: Authors' calculations and analysis.

**EXHIBIT 3**
**Summary Results For The Six Scenarios For Ten-Year Planning Horizon And One Million Population For Baseline Elasticity**

| Scenario | Deaths | Deaths averted (compared with scenario A) | Discounted treatment costs ($) | Discounted cost of infection ($) | Treatment cost per death averted ($)[a] | Subsidy cost per death averted ($)[a] |
|---|---|---|---|---|---|---|
| A | 123,795 | | 3,597,358 | 890,435,270 | | |
| B | 118,777 | 5,019 | 9,250,653 | 852,123,527 | 1,230 | 896 |
| C | 115,190 | 8,605 | 20,884,528 | 823,912,259 | 2,166 | 1,858 |
| D | 117,262 | 6,534 | 17,209,239 | 841,741,586 | 2,330 | 1,996 |
| E | 115,879 | 7,916 | 9,036,006 | 832,351,283 | 780 | 577 |
| F | 108,966 | 14,830 | 19,780,901 | 780,373,241 | 1,225 | 1,064 |

**SOURCE:** Authors' calculations and analysis.

[a] Costs and deaths averted are incremental to baseline and are discounted at a constant annual rate of 3 percent.

of averting a death in terms of the subsidy applied to increase ACT use was $896.

A full subsidy of one dollar per treatment course of ACT in scenario C was found to avert 8,605 deaths over the ten-year horizon at a treatment cost of roughly $2,166 per death averted relative to the no-subsidy scenario. The subsidy cost per death averted was $1,858.[16]

Scenario D (the delayed subsidy after some period of AMT and PMT) resulted in fewer deaths compared with scenario A but at a greater treatment cost (relative to a subsidy policy implemented today) of $2,330 and a subsidy cost of $1,996 per death averted.

Scenarios E and F were by far the most effective at reducing deaths and lowering burden at a low cost. A partial subsidy to two ACTs reduced roughly 60 percent more deaths at 50–60 percent of the cost of equivalent subsidy programs that relied on a single ACT. The subsidy cost of an averted death was 57–65 percent of the equivalent cost for scenarios in which a single ACT was used.

Next we tested the sensitivity of these results to the demand elasticity parameter (Exhibit 4). When demand was relatively unresponsive to price (elasticity of −2), relatively fewer deaths were averted with a partial subsidy because of the failure to drive out AMT and PMT. The incremental treatment cost per death averted was lowest for demand elasticity of −2 and greatest for elasticity of −4.

Under a demand elasticity assumption of −2, a full subsidy to ACTs increased ACT usage to 15 percent and averted roughly 9,000 deaths relative to baseline. Treatment cost per death averted was $1,245. Under the demand elasticity assumption of −4, ACT usage under the full subsidy increased to 78 percent (exceeding the Abuja targets) while completely shutting out compromising monotherapy.[17] Treatment cost per death averted increased to $3,625, and subsidy cost per death averted increased to $3,060 because of the greater likelihood of emergence of resistance to the ACT combination.

Two results remained qualitatively unchanged regardless of the responsiveness

**EXHIBIT 4**
**Sensitivity Analysis With Respect To Demand Elasticity For The Six Scenarios For Ten-Year Planning Horizon And One Million Population**

| Scenario | Deaths averted (compared with scenario A) | | Treatment cost per death averted ($)[a] | | Subsidy cost per death averted ($)[a] | |
|---|---|---|---|---|---|---|
| | Elasticity −2 | Elasticity −4 | Elasticity −2 | Elasticity −4 | Elasticity −2 | Elasticity −4 |
| B | 2,939 | 7,732 | 846 | 1,698 | 687 | 1,180 |
| C | 5,246 | 8,939 | 1,245 | 3,625 | 1,126 | 3,060 |
| D | 3,703 | 6,724 | 1,443 | 3,939 | 1,301 | 3,322 |
| E | 5,485 | 12,665 | 444 | 1,023 | 373 | 720 |
| F | 8,141 | 17,379 | 802 | 1,780 | 736 | 1,517 |

**SOURCE:** Authors' calculations and analysis.

[a] Costs and deaths averted are incremental to baseline and are discounted at a constant annual rate of 3 percent.

of demand to price. First, a delay in instituting a subsidy program was always inferior both in saving lives and in the cost of averting deaths compared with all other scenarios. Second, the use of two combinations averted more deaths and was more cost-effective than use of a single combination at equivalent subsidy levels.

## Discussion And Policy Implications

The results indicate that a subsidy of ACTs is likely to extend the therapeutic life of artemisinin and partner drugs even if the subsidy results in expanding use of ACTs for reasonable ranges of own- and cross-price elasticity of treatment demand. Although the emergence of resistance is delayed by the use of combinations, it is highly sensitive to the choice of partner drugs used with artemisinin. Using a partner antimalarial to which resistance has already evolved or is likely to evolve quickly is likely to lead to more rapid emergence of resistance to the combination. This finding is consistent with those of other recent studies.[18]

Contemporaneous use of a compromising monotherapy (either AMT or PMT) was not as detrimental to the emergence of resistance as one might have anticipated. Although resistance emerged faster with contemporaneous compromising monotherapy (scenario B), the emergence and spread of resistance was limited by the deployment of ACTs. This aspect of the model's results should be explored further in future research.

The model's results indicate that when treatment coverage is relatively less sensitive to drug price, moving from the partial to the full subsidy results in roughly doubling the number of deaths averted. However, with a more elastic demand specification, a full subsidy averted only roughly 16 percent more deaths relative to the partial subsidy. This is a consequence of our motivating argument—that greater use of ACTs could expedite the emergence of resistance. Depending on the level of demand elasticity (which would have to be empirically determined), it is possible to identify a level of subsidy at which the greatest number of deaths is

averted. It is important to recognize that a larger subsidy is not necessarily a good thing if it excessively encourages the use and misuse of ACTs.

We found that a delayed introduction of a full subsidy program was possibly the worst scenario in both averted deaths and cost-effectiveness. The delay would permit continued use of AMT and PMT and emergence of low-level resistance, which would then be magnified through intense selection pressure with the introduction of a full subsidy.

■ **Implications.** An important implication of the results is that using a single combination in all regions places greater selection pressure on parasites to become resistant to that combination. Use of different combinations relieves the selection pressure for resistance to any single combination to evolve. In general, the idea of using the same ACT combination worldwide deserves serious reconsideration. Also, different ACT combinations might, if priced lower than monotherapies, be effective in driving out monotherapies by offering consumers a choice of different antimalarials with different dosing schedules and other attributes.

A possible secondary benefit of increasing ACT use is the potentially reduced selection pressure for chloroquine (CQ) resistance, but this not explicitly modeled in this paper. ACT would clear CQ-resistant strains and reduce the frequency of CQ resistance, and after some time, CQ might become useful again.[19] However, since CQ resistance could be reintroduced from another country, a switch to a CQ-only strategy would be undesirable because resistance would probably return to its former frequency. A better strategy would be to continue to use ACTs and CQ in roughly equal amounts so that ACTs reduce the selection pressure on CQ, and CQ reduces the selection pressure on ACTs. Simultaneous use of two agents reduces the selective advantage of resistance to either agent and benefits both. These benefits arise because of the interactions with a third player: drug-sensitive malaria. Neither CQ-resistant nor ACT-resistant malaria has an advantage over drug-sensitive malaria when no drug is used.

The same principles apply to the simultaneous use of two ACT agents, but in that case, the benefits of decreased selection pressure can additionally delay the time to the appearance of resistance to each ACT combination. In principle, contemporaneous use of three or more ACT agents would be even better than two because resistance to each antimalarial would be reduced by the use of every other antimalarial in competition relative to drug-sensitive malaria. We did not evaluate whether the use of an ACT triple (artemesinin combined with two partner drugs) would be more effective than the use of two ACT doubles. The relevant trade-offs are the longer delay in the appearance of malaria that is resistant to all drugs in the combination weighed against the expense of subsidizing each additional agent in the combination and the added selection pressure from increasing the use of each agent in the combination.

■ **Study caveats.** A number of caveats apply to these results. First, they are relevant only from a qualitative standpoint; the quantitative aspects of deaths averted,

time to emergence of resistance, and other such outcomes are highly sensitive to model parameters. Also, more-complex models are needed to explore specific phenomena, such as the effects of ACTs on transmission potential. For instance, increased use of ACTs could result in greatly reduced transmission by reducing both the total number of circulating parasites (included in this model) and the gametocytes in circulation because of the effect of the artesunate in ACTs (not considered here).[20] Also, within the context of a particular structure of consumer demand, we find that the cost-effectiveness results are sensitive to the responsiveness of demand to price. If demand is highly responsive, additional lives are saved at the cost of an earlier spread of artemisinin-resistant strains of plasmodium. Within the assumptions used here, a global subsidy would be cost-effective across a range of plausible demand elasticities. However, the attractiveness of a global subsidy would be somewhat reduced when demand is highly responsive. The increase in ACT use in response to the subsidy would speed the development of resistance so much that more lives would be lost from ineffective antimalarials than would be gained from the increased utilization.

Second, optimal policy is likely to be affected by the potential availability of cheaper synthetic ACT combinations in the near future. Such combinations might lower the value of introducing expensive versions of the combination drugs today if other drugs become available. However, AMT has the potential to introduce cross-resistance that could reduce the efficacy of these new, synthetic ACTs. To quantitatively consider the impact of the availability of synthetic ACTs on optimal policy today, one would need to know (with some degree of approximation) the expected date of arrival of the new synthetic antimalarials and their likely efficacy.

Another unknown is the potential availability of a malaria vaccine. The impact of vaccine availability on optimal treatment policy today is similarly ambiguous. On the one hand, a vaccine lowers the benefits of an effective drug in the future, since the caseload will be reduced. However, an effective vaccine could, in combination with effective treatment, eradicate the disease in some areas. Thus, interesting nonlinearities in the benefit function might alter the costs of resistance and influence current use policies.

T HE BASIC OBJECTIVES OF THIS STUDY were to examine whether a subsidy for ACTs would save lives and reduce malaria (compared with a counterfactual in which AMT and PMT would be used) and, if so, at what cost. We reached three main conclusions: (1) A subsidy for ACTs—even a partial one— would save lives even if it hastened the arrival of parasite resistance to artemisinin-based drugs. This finding has important implications for moving ahead on ACT subsidies. The difficulty of funding a full subsidy for ACTs should not stand in the way of instituting a more modest subsidy immediately. Furthermore, the introduction of price subsidies should be accompanied by studies of demand response and of the quality of malaria service delivery, which would enable a more precise deter-

mination of the optimal subsidy level. (2) A delay (even by two years) in instituting a subsidy for ACTs would exacerbate resistance engendered by use of AMT and PMT prior to the introduction of a subsidy and would lead to faster resistance to ACTs. Therefore, a subsidy to ACTs should be implemented sooner rather than later. (3) A global subsidy for two or more ACTs is likely to be far more effective in delaying the onset of resistance and saving lives than reliance on a single or a few combinations. The global subsidy program should support locally appropriate combination and treatment strategies, while keeping in mind the importance of transboundary spillovers of actions and decisions undertaken by any single country.

These conclusions suggest that a global subsidy for ACTs will not only save lives but also buy time. The rationale for considering ACT effectiveness a global public good is that resistance can arise in any single country and that use of AMT or even ACT can hasten the rate at which the resistant strain proliferates worldwide. A worst-case scenario would be one in which poor policy making results in the emergence of artemisinin resistance in a single country or region. This would compromise treatment in all countries where ACTs are introduced. Surveillance is therefore needed so that the global subsidy program can be nimble in detecting emergence of resistance and changing drug combinations.

## NOTES

1. K.J. Arrow et al., eds., *Saving Lives, Buying Time: Economics of Malaria Drugs in an Age of Resistance* (Washington: Institute of Medicine, 2004).

2. These deliberations were held during a meeting of the Roll Back Malaria (RBM) Finance and Resources Working Group, 8–9 September 2004, in Washington, D.C.

3. Arrow et al., eds., *Saving Lives, Buying Time*, 84.

4. Support for the public-goods argument could be bolstered if effective treatment with ACTs were to result in reductions in malaria transmission. Evidence of a transmission-reduction effect has been found in Southeast Asia but has not been confirmed in sub-Saharan Africa. See F. Nosten et al., "Effects of Artesunate-Mefloquine Combination on Incidence of *Plasmodium falciparum* Malaria and Mefloquine Resistance in Western Thailand: A Prospective Study," *Lancet* 356, no. 9226 (2000): 297–302.

5. The effectiveness of antimalarials (and other drugs to treat infectious diseases) is not a pure public good, which is defined as being nonexcludable and nonrival in consumption. Rather, it is nonexcludable but rival in consumption (that is, one individual's use of antimalarial effectiveness diminishes its effectiveness for others) and can be classified as a global common property resource, as are fisheries and climate stabil-

ity. The extent to which antimalarial effectiveness is a public good also depends on the extent to which resistance is transmitted across borders. Since resistance to artemisinin compounds has not been detected, it is difficult to predict whether resistance will arise independently in several locations or occur in a few locations before spreading around the globe, as was the case with commonly encountered mutations that conferred resistance to chloroquine (pfcrt) and sulfadoxine-pyrimethamine (dhfr and dhps). If the latter were the case, then the resistance that could arise in a single country or region could jeopardize the value of artemisinin drugs in all countries where they will be used.

6. R. Smith et al., "Communicable Disease Control: A 'Global Public Good' Perspective," *Health Policy and Planning* 19, no. 5 (2004): 271–278; and R.D. Smith and J. Coast, "Antimicrobial Resistance: A Global Response," *Bulletin of the World Health Organization* 80, no. 2 (2002): 126–133.

7. M.B. Ettling and D.S. Shepard, "Economic Cost of Malaria in Rwanda," *Tropical Medicine and Parasitology* 42, no. 3 (1991): 214–218.

8. Although improved compliance is generally assumed to lower the likelihood of emergence of resistance, this might be true only for de novo resistance that emerges in infected individuals receiving antimalarials, and not for epidemic resistance, which is transmitted between individuals.

9. J.C. Koella, "On the Use of Mathematical Models of Malaria Transmission," *Acta Tropica* 49, no. 1 (1991): 1–25; S. Bonhoeffer, M. Lipsitch, and B.R. Levin, "Evaluating Treatment Protocols to Prevent Antibiotic Resistance," *Proceedings of the National Academy of Sciences (USA)* 94, no. 22 (1997): 12106–12111; J. Koella and R. Antia, "Epidemiological Models for the Spread of Anti-Malarial Resistance," *Malaria Journal* 2, no. 1 (2003): 3; and R. Laxminarayan, "Act Now or Later? Economics of Malaria Resistance," *American Journal of Tropical Medicine and Hygiene* 71, no. 2 Supp. (2004): 187–195. Details of the model are available in Appendix A, at http://content.health affairs.org/cgi/content/full/25/2/325/DC1.

10. I.M. Hastings, "A Model for the Origins and Spread of Drug-Resistant Malaria," *Parasitology* 115, Part 2 (1997): 133–141.

11. World Health Organization, *World Malaria Report 2005* (Geneva: WHO, 2005).

12. Own-price elasticity refers to the percentage increase in the demand for a drug in response to a 1 percent decrease in its own price. Cross-price elasticity refers to the percentage increase in the demand for a drug in response to a 1 percent decrease in the price of a different antimalarial. Details of the demand specification are available in Appendix B; see Note 9.

13. Among the other relevant factors is household income level. A benefit of the proposed subsidy is to increase access to antimalarials by the poorest. Yet these same patients might be most likely to misuse the drug and speed the development of resistant strains. On the links between poverty and febrile illness, most of which is probably malaria, see D. Filmer, "Fever and Its Treatment among the More and Less Poor in Sub-Saharan Africa," Policy Research Working Paper no. 2798 (Washington: World Bank, 2002).

14. Laxminarayan, "Act Now or Later?" Also, see Appendix A, as in Note 9.

15. See Appendix B for derivation of these treatment coverage levels, as in Note 9.

16. In scenarios C and F, the incremental subsidy costs per disability-adjusted life year (DALY) averted exceed the incremental treatment costs per DALY averted. This is possible because subsidy costs (unlike treatment costs) are zero for the baseline scenario A.

17. "Abuja targets" refers to targets for malaria treatment that were set in Abuja, Nigeria, by the African heads of state in 2000.

18. W.M. Watkins, C.H. Sibley, and I.M. Hastings, "The Search for Effective and Sustainable Treatments for *Plasmodium falciparum* Malaria in Africa: A Model of the Selection of Resistance by Antifolate Drugs and Their Combinations," *American Journal of Tropical Medicine and Hygiene* 72, no. 2 (2005): 163–173.

19. M.K. Laufer and C.V. Plowe, "Withdrawing Antimalarial Drugs: Impact on Parasite Resistance and Implications for Malaria Treatment Policies," *Drug Resistance Updates* 7, nos. 4–5 (2004): 279–288.

20. Reduced transmission with effective treatment has been shown to be the case with the treatment of tuberculosis. See S. Blower, K. Koelle, and T. Lietman, "Antibiotic Resistance—To Treat…" (letter), *Nature Medicine* 5, no. 4 (1999): 358.