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Should New Antimalarial Drugs Be Subsidized?

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Abstract

We use analytical and numerical models to explain and quantify the welfare effects of subsidies for artemisinin combination treatments (ACTs), a valuable new class of antimalarial drugs. There are two (second-best) efficiency rationales for such subsidies: by expanding drug use, they reduce infection transmission from one individual to another, and they slow the evolution of drug resistance by deterring use of substitute monotherapy drugs for which resistance emerges more rapidly than for ACTs.

Our analysis merges epidemiological models of malaria transmission among individuals and mosquitoes, evolution of drug resistance, and economic models of the demand for alternative drugs; parameter values for the simulations are representative of malaria prevalence in sub-Saharan Africa. We find that large subsidies for ACT are welfare improving across many plausible scenarios for malaria transmission, drug-demand elasticities, and evolution of drug resistance; the benefits of the policy are often several times larger than the costs.

Key Words: antimalarial drugs, resistance externality, transmission externality, subsidies, welfare effects

JEL Classification Numbers: I18, H23, O15

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1. Introduction

Malaria continues to be a serious global health challenge that causes an estimated 300 million to 500 million infections and more than 2 million deaths each year; approximately 90 percent of deaths occur in sub-Saharan Africa (Snow et al., 2005; Roll Back Malaria et al., 2005). The rapidly declining effectiveness of chloroquine (CQ) and other antimalarial drugs is a major cause of increased morbidity and mortality from malaria in recent decades (Trape et al., 1998; Trape, 2001). A new class of antimalarials, called artemisinins, to which little or no resistance has arisen, is now widely available.[1] Although artemisinins are more costly than other drugs, they provide effective treatment and the potential to roll back malaria. However, as with other drugs, resistance to artemisinin may evolve quickly, especially if this class is used intensively as a monotherapy treatment (Jambou et al., 2005).

The World Health Organization (WHO, 2001) has recommended that artemisinin be used in combination with a partner drug, unrelated in mechanism of action and genetic bases of resistance, so that a single mutation cannot encode resistance to both components. If artemisinin combination treatments (ACTs) are used instead of artemisinin monotherapy treatments (AMTs) and the partner drug, this should slow down the emergence of antimalarial resistance. However, the WHO guidelines are routinely flouted, given that AMTs and other monotherapies are much less expensive than ACTs. In response to this problem, a recent Institute of Medicine report (Arrow et al., 2004) recommended establishing an international fund to buy ACTs at producer cost and resell them at a small fraction of that cost.

On economic-efficiency grounds there is a second-best case for subsidizing ACTs, because the ideal policy of taxing AMTs and other antimalarials according to the marginal external cost from the elevated risk of resistance evolution is infeasible, given their widespread use in the informal sector. The

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[1] Artemisinins are derived from the plant *Artemisia annua*, which is cultivated in China and Vietnam. Although the plant had been used for centuries as a treatment for fevers, the compound that acted against malaria was not discovered until the 1970s (Hien et al., 1993).

efficiency argument is further strengthened by the positive externality to the extent that effective treatment by one individual reduces the risk of infection transmission to other individuals. Nonetheless, it is still critical to understand what *level* of subsidy might be appropriate, and to what extent this varies with malaria prevalence across different regions, the risk of resistance evolution, drug-demand responses, the extent of donor financing, the cost of illness, and other factors.

Although some theoretical literature exists on optimal drug taxes and subsidies (Philipson and Mechoulan, 2003; Rudholm, 2002), there have been few attempts to empirically apply this theory, and none in the context of antimalarial drugs. This paper seeks to fill this gap. We begin with a static, analytical representation that provides insight into the resistance and transmission externalities and the welfare effects of ACT subsidies. Following that, we integrate a dynamic model of malaria transmission between humans and mosquitoes, and the spread of drug resistance, adapted from recent epidemiological literature, into a utility-maximizing model of drug demand, to simulate the effects of ACT subsidies. Calibrating the model is challenging because of uncertainty over, and spatial variability of, several epidemiological parameters, and the difficulty of gauging the demand response to very large price changes. Our objective is therefore to identify the circumstances under which large, recently proposed ACT subsidies might be warranted on efficiency grounds, rather than to provide finely tuned estimates of optimal subsidies.

We estimate that large subsidies for ACT are efficiency enhancing in many scenarios. For modest subsidies, the effect is mainly to crowd out the use of monotherapies and increase the average useful life of drugs, whereas for large subsidies, overall drug demand starts to expand, thereby lowering disease transmission. These two sources of efficiency gain outweigh the distortionary cost of the subsidy in most cases. In fact, overall discounted benefits (over a 20-year horizon) are often several times higher than discounted costs; moreover, welfare gains are much larger still if external donors financing the program enjoy significant altruistic benefits. The main exception when large subsidies are not warranted by externalities (aside from when drug-demand responses are extremely limited) is when transmission rates are very high (in excess of about 60 to 80 infectious bites per year); in this case, expanding ACT use has little impact on reducing the infection rate, since treated individuals quickly become reinfected and efficiency gains from the treatment externality are small.

2. Analytical Model

We begin with a theoretical model to help interpret the transmission and resistance externalities and the welfare effects of ACT subsidies. The model is highly simplified: it is static, incorporates only two drugs, and does not distinguish immune individuals from those susceptible to infection; these and other restrictions are relaxed in the subsequent simulation model.

2.1. Assumptions

We adopt a homogeneous-agent model where the agent represents an average over people of different ages within a region of given malaria prevalence. Utility is defined by:

(2.1a) $u = u\{\bar{n}^{INF}, x, E\}, \qquad E = E\{\bar{e}_C A_C, \bar{e}_M A_M\}$

(2.1b) $e_C = e_C\{\bar{A}_C, \bar{A}_M\}, \qquad e_M = e_M\{\bar{A}_C, \bar{A}_M\}, \qquad \bar{n}^{INF} = n^{INF}\{\bar{e}_C \bar{A}_C, \bar{e}_M \bar{A}_M\}$

where variables are per capita, present values over the period, and a bar denotes a population-wide variable that is exogenous to the individual.

Utility $u\{.\}$ declines with instances of malaria infection n^{INF}, which cause incapacitation, elevated mortality risk, and other morbidity complications (for now, assume all infections are symptomatic); utility increases with a general consumption good x and subutility $E\{.\}$ from effective drug treatments. E increases with consumption of artemisinin combination and monotherapy treatments, denoted A_i ($i = C, M$). $e_i\{.\}$ is the effectiveness of drug i, or the probability that the treatment will kill the infection; e_i declines as drug resistance evolves during the period in response to population-wide use of both drugs ($e_{i1}, e_{i2} < 0$, $0 \le e_i \le 1$).[2] We assume that drugs are imperfect substitutes even if they have the same effectiveness (e.g., because of differences in access costs, consumer familiarity, risk of side-effects). Finally, we assume the infection transmission rate $\bar{n}^{INF}\{.\}$ declines with the effective drug treatments of other households.

The household budget constraint is:

(2.2) $(p_C - s)A_C + p_M A_M + p_x x = INC$

where INC is (fixed) household income and p_C, p_M, and p_x denote producer prices of the two drugs and the general good and equal (constant) marginal supply costs;[3] s is a per-unit subsidy for ACT. $p_C > p_M$ because of the higher cost of ingredients for producing ACT.

We assume that the burden of the subsidy is borne by foreign donors who enjoy an altruistic benefit of μ per $1 of spending; the net (global) cost of financing the subsidy is therefore $(1-\mu)s\bar{A}_C$.[4]

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[2] That is, a parasite that becomes resistant to ACT is more likely to also be resistant to AMT, and vice versa, given that the two drugs have a common ingredient (artemisinin).

[3] In developed countries, pharmaceutical companies price patented drugs above marginal costs to recoup R&D investments, while at the margin drug costs may be borne by third parties rather than consumers. We ignore these complications, given that artemisinin drugs in sub-Saharan Africa are not restricted by patents, and they are mainly purchased directly by individuals with out-of-pocket payments.

[4] There has recently been much discussion of the potential use of internationally coordinated taxes (e.g., on international air travel in high-income countries) as a source of finance for measures to counter malaria and other

However, for most of our simulations below, we ignore altruistic preferences and assume $\mu = 0$, given that their qualitative effect on the optimal subsidy is straightforward and that the extent of altruism is difficult to gauge empirically.

Optimizing (2.1) subject to (2.2) yields the agent's first-order conditions:

$$(2.3) \qquad \frac{u_E}{u_x}\frac{\partial E}{\partial A_C}e_C = p_C - s, \qquad \frac{u_E}{u_x}\frac{\partial E}{\partial A_M}e_M = p_M$$

Agents consume drugs up to the point where the marginal private benefit (in consumption equivalents), adjusted for drug effectiveness, equals the market price. Note that the marginal benefit from treatment $p_C - s$ will be less than the cost of an untreated illness $-u_{n^{INF}}/u_x$ because of, for example, access costs and illness prior to recovery from treatment (thus, not all symptomatic malaria infections are treated, even if drug prices are less than the cost of illness). We assume that marginal utility from drug treatment is declining (e.g., because of rising access costs for individuals in rural areas) such that drug-demand curves are downward sloping.

2.2. Welfare Effects and the Optimal Level of ACT Subsidy

From totally differentiating the indirect utility function, the welfare effect of an incremental increase in *s* is (see Appendix):

$$(2.4a) \quad (EXT_C^T - EXT_C^R - s)\frac{dA_C}{ds} - (EXT_M^T - EXT_M^R)\left(-\frac{dA_M}{ds}\right) + \mu\left(A_C + s\frac{dA_C}{ds}\right)$$

$$(2.4b) \quad EXT_i^T = \frac{u_{\bar{n}^{INF}}}{u_x}\frac{\partial \bar{n}^{INF}}{\partial A_i}, \; EXT_i^R = -\sum_j\left(\frac{u_E}{u_x}\frac{\partial E}{\partial \bar{e}_j} + \frac{u_{\bar{n}^{INF}}}{u_x}\frac{\partial \bar{n}^{INF}}{\partial \bar{e}_j}\right)\left(-\frac{\partial \bar{e}_j}{\partial A_i}\right), \; i, j = C, M$$

EXT_i^T is the marginal external benefit due to use of drug *i* on reducing disease transmission for given drug effectiveness; it equals the per capita reduction in infection risk to others, $-\partial \bar{n}^{INF}/\partial A_i$, times the cost of illness. EXT_i^R is the marginal external cost of using drug *i* due to reduced future drug effectiveness. A unit increase in A_i reduces the effectiveness of drug *j* by $-\partial \bar{e}_j/\partial A_i$; each unit reduction in drug effectiveness reduces utility by $-u_E \cdot \partial E/\partial \bar{e}_j$, because of the reduced likelihood of successful treatment, and also by $-u_{\bar{n}^{INF}} \cdot \partial \bar{n}^{INF}/\partial \bar{e}_j$, because of the greater risk of infection transmission from other agents using drugs.

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infectious diseases (e.g., Atkinson 2005). An alternative interpretation of $\mu > 0$ is that, from a global welfare perspective, the donor may have a lower social welfare weight than the recipient country.

Figure 1 illustrates the first two components of the welfare change in (2.4a), for the case when $EXT_M^R > EXT_C^R$ and $EXT_i^R > EXT_i^T$. In each panel, the marginal social cost of drug use exceeds the producer cost by $EXT_i^R - EXT_i^T$, and for ACT there is a further wedge of *s* between the producer cost and the demand price. An incremental increase in *s* induces a downward movement along the demand curve for ACT in the top panel, inducing a welfare loss, shown by the shaded rectangle with base dA_C / ds and height $EXT_C^R - EXT_C^T + s$. However, in the lower panel the demand curve for AMT shifts in, causing a welfare gain, shown by the rectangle with base $-dA_M / ds$ and height $EXT_M^R - EXT_M^T$.

The third component in (2.4a) is a welfare gain due to the possible altruistic benefits accruing to donor countries; it equals the marginal increase in the subsidy payment times μ.

Equating (2.4a) to zero yields the theoretically optimal subsidy

$$s^* = \frac{\beta(EXT_M^R - EXT_M^T) - (EXT_C^R - EXT_C^T) + \mu A_C / (dA_C ds)}{1 - \mu} \quad \text{(2.5a)}$$

$$\beta = -\frac{dA_M / ds}{dA_C / ds} \quad \text{(2.5b)}$$

where β defines the (marginal) crowding out of other drugs—that is, the reduction in A_M relative to the increase in demand for A_C. If there were no resistance and $\mu = 0$, then $s^* = EXT_C^T - \beta \cdot EXT_M^T$, which is positive with imperfect crowding out ($\beta < 1$). The optimal subsidy is higher still with resistance evolution (as long as β is not too small), and with altruistic preferences.

3. Dynamic, Numerical Model

Although (2.4) and (2.5) provide useful intuition, they cannot be computed because resistance, disease transmission, and drug effectiveness (and hence EXT_i^T and EXT_i^R) vary endogenously with drug use; moreover, the prior model provides only a steady-state representation of complex dynamic processes and considers only two drugs. Therefore, we now adapt a dynamic formulation of infection transmission and resistance evolution from recent epidemiological literature (Bonhoeffer et al., 1997; Koella and Antia, 2003; Laxminarayan, 2004; Smith and McKenzie, 2004) and merge it with demand functions for three alternative drugs; after compiling the available evidence to parameterize the model, we solve by numerical simulation.

3.1. Epidemiological Framework

We describe malaria transmission first with no resistance and one drug, then with resistance distinguishing three drugs. We then discuss how the transmission rate depends on mosquito characteristics.

3.1.1. Disease transmission without drug resistance. At any particular point in time, *t*, the population is divided into three groups, $N = N^{SUS} + N^{INF} + N^{IMM}$; N^{SUS} includes people susceptible to infection, N^{INF} are those who are infected, whether symptomatic or not or being treated or not; and N^{IMM} are those who have recently recovered spontaneously (i.e., without treatment) from an infection and are now immune.[5] The rates of change for the population subgroups are:

(3.1a) $$\frac{dN^{SUS}}{dt} = -(h + \delta^{N})N^{SUS} + a\rho^{TR}N^{INF} + \gamma N^{IMM} + B$$

(3.1b) $$\frac{dN^{INF}}{dt} = hN^{SUS} - (a\rho^{TR} + (1-a)\rho^{SP} + \delta^{INF} + \delta^{N})N^{INF}$$

(3.1c) $$\frac{dN^{IMM}}{dt} = (1-a)\rho^{SP}N^{INF} - (\gamma + \delta^{N})N^{IMM}$$

where δ^{N}, ρ^{TR}, ρ^{SP}, and δ^{INF} are exogenous and *h*, *a*, γ, and *B* are endogenous (see below).

h is the transmission rate—that is, the rate at which the susceptible population becomes infected; γ is the rate at which people lose immunity and become susceptible again (the inverse of the average duration of immunity); and *a* is the fraction of infected individuals receiving drug treatment, which equals the fraction of infected people who are symptomatic times the drug coverage rate of these individuals. ρ^{TR} is the recovery rate for treated individuals (the inverse of time taken for drugs to cure an infection) who go straight to being susceptible,[6] and ρ^{SP} is the spontaneous recovery rate, where $\rho^{SP} < \rho^{TR}$. δ^{INF} and δ^{N} are the mortality rates from malaria and all other causes of death. To focus on a fixed population size, we assume that malaria-specific and other deaths are exactly balanced by new births *B*, which start out as susceptible (we assume that infants have no immunity), therefore, $B = \delta^{INF}N^{INF} + \delta^{N}N$ (results are not

[5] The immune group is commonly referred to as resistant in SIR (susceptible, infected, resistant) models of infection transmission; however, we use different terminology because we later need to distinguish those who are resistant or immune to infection from those who are resistant to drugs.

[6] This is consistent with most evidence (Pringle and Avery-Jones, 1966; Cornille-Brogger et al., 1978), although some models allow for some period of immunity following treatment (e.g., Koella and Antia, 2003).

sensitive to other assumptions). All variables and parameters represent averages for people of different ages within the population group.[7]

3.1.2. Incorporating drug resistance. We now distinguish three drugs: ACT, AMT, and PMT (a partner drug whose costs are consistent with sulfadoxine-pyrimethamine) denoted *i* = *C*, *M*, and *P* where ACT combines *M* and *P*. Resistance arises spontaneously through genetic mutation when individuals take drugs, and it can be transmitted to others through mosquito bites. The infected population is divided into four groups, $N^{INF} = N_W^{INF} + N_M^{INF} + N_P^{INF} + N_C^{INF}$, where N_W^{INF} is those infected with a nonresistant or wild-type infection, N_M^{INF} and N_P^{INF} are those whose infections are resistant to either *M* or *P*, and N_C^{INF} is those whose infections are resistant to both drugs, and hence also ACT.

Population groups now change according to:

(3.2a) $$\frac{dN^{SUS}}{dt} = -(h+\delta^N)N^{SUS} + \rho^{TR}N_W^{INF}\Sigma_i a_i(1-r_i) + \rho^{TR}N_M^{INF}(a_P+a_C)(1-r_P a_P) + \rho^{TR}N_P^{INF}(a_M+a_C)(1-r_M a_M) + \gamma N^{IMM} + B$$

(3.2b) $$\frac{dN_W^{INF}}{dt} = h_W N^{SUS} - \rho^{TR}N_W^{INF}\Sigma_i a_i - N_W^{INF}(\rho_W^{SP}(1-\Sigma_i a_i) + \delta^{INF} + \delta^N)$$

(3.2c) $$\frac{dN_M^{INF}}{dt} = h_M N^{SUS} - \rho^{TR}N_M^{INF}(a_P+a_C) + \rho^{TR}N_W^{INF}r_M a_M - N_M^{INF}(\rho_M^{SP}(1-a_P-a_C) + \delta^{INF} + \delta^N)$$

(3.2d) $$\frac{dN_P^{INF}}{dt} = h_P N^{SUS} - \rho^{TR}N_P^{INF}(a_M+a_C) + \rho^{TR}N_W^{INF}r_P a_P - N_P^{INF}(\rho_P^{SP}(1-a_M-a_C) + \delta^{INF} + \delta^N)$$

(3.2e) $$\frac{dN_C^{INF}}{dt} = h_C N^{SUS} + \rho^{TR}(N_W^{INF}r_M r_P a_C + N_M^{INF}r_P(a_P+a_C) + N_P^{INF}r_M(a_M+a_C)) - N_C^{INF}(\rho_C^{SP} + \delta^{INF} + \delta^N)$$

(3.2f) $$\frac{dN^{IMM}}{dt} = \rho_W^{SP}N_W^{INF}(1-\Sigma_i a_i) + \rho_M^{SP}N_M^{INF}(1-a_P-a_C) + \rho_P^{SP}N_P^{INF}(1-a_M-a_C) + \rho_C^{SP}N_C^{INF} - (\gamma+\delta^N)N^{IMM}$$

[7] Children are far more susceptible to malaria infection and mortality than adults, because people build up immunity with instances of infection over the life cycle. If we were studying a population with changing demographics over time, we would need to factor this into our choice of parameter values.

a_i is the fraction of infected individuals using drug *i*, r_i is the probability that use of drug *i* will spontaneously lead to a mutation that is resistant to that drug, and we assume mortality and treatment recovery rates are the same across subgroups of infected individuals.[8] However $\rho_C^{SP} > \rho_M^{SP}, \rho_P^{SP} > \rho_W^{SP}$ —that is, the spontaneous recovery rate is greater for resistant than for wild-type infections, and is greatest for infections resistant to both drugs; resistant strains therefore face a "fitness cost" and would eventually die out if all drug use ceased (Hastings and Donnelly, 2005).

The essential difference between (3.2) and (3.1) is that some people using drugs who are infected with the wild-type strain now become resistant to that drug and move into the N_M^{INF}, N_P^{INF} or N_C^{INF} subgroups. In addition, of those who are resistant to one of the monotherapies, some who use the other monotherapy or ACT move to the susceptible group, while others also become resistant to that drug and move to the N_C^{INF} group. Once in the N_C^{INF} group, individuals are resistant to all drugs and can only recover spontaneously.

3.1.3. Mosquito characteristics and the transmission rate. Suppose ρ is the number of times a mosquito bites a human each day, b_1 is the probability that biting an infected human will infect the mosquito, $n_i^{INF} = N_i^{INF} / N$ is the fraction of humans who are infectious with strain *i*, and δ^{mos} is the mosquito mortality rate. Then the probability that a mosquito will become infected with strain *i* during its life is (Smith 2004):[9]

$$\text{(3.3a)} \quad \pi_i^{INF} = \frac{\rho b_1 n_i^{INF}}{\delta^{mos} + \rho b_1 n_i^{INF}}$$

A latency period of τ days is required before the virus forms sporozoites in the salivary glands, making it possible for the mosquito to transmit the infection; the likelihood that the mosquito will become infectious to humans during its life is therefore $e^{-\tau\delta^{mos}}\pi_i^{INF}$. Since a mosquito lives another $1/\delta^{mos}$ days, the expected number of infectious bites during its life is $e^{-\tau\delta^{mos}}\pi_i^{INF}\rho/\delta^{mos}$. The number of infectious bites received by each human per day, or the transmission rate, is

[8] Even infected people who are not symptomatic face an elevated risk of mortality because the presence of parasites in the bloodstream increases susceptibility to other diseases (Greenwood, 1987).

[9] We do not consider the possibility of superinfection when a mosquito or human becomes coinfected by a second strain; its effects on δ^{INF}, r_i, and ρ_i^{SP} are not well understood, although they appear to be small (Koella and Antia, 2003).

(3.3b) $h_i = b_2\, m e^{-\tau\delta^{mos}} \pi_i^{INF} \rho / \delta^{mos}$

where m is the number of (female) mosquitoes that emerge per human per day, and b_2 is the probability that a bite from an infectious mosquito will infect a human.[10] Since the transmission rate rises with the infection rate, resistant strains evolve exponentially, or conversely, drug effectiveness remains close to unity for a while, then declines sharply before stabilizing above zero (because of spontaneous recovery from resistant strains, which tends to prevent that strain from becoming 100 percent of all infections).

3.2. Economic Model

3.2.1. Household utility and drug demand. We adopt the following nested, constant elasticity of substitution (CES) utility function defined over a period of duration $\bar{t}$, where θ is the daily discount rate:

(3.4a) $$U = \int_0^{\bar{t}} e^{-\theta t} \left\{ \left[x^{\frac{\sigma_u - 1}{\sigma_u}} + E^{\frac{\sigma_u - 1}{\sigma_u}} \right]^{\frac{\sigma_u}{\sigma_u - 1}} - \alpha^{COST} \bar{n}^{INF} \right\} dt, \qquad i = W, M, P, C$$

(3.4b) $$\alpha^{COST} / u_x = k + v\delta^{INF}$$

(3.4c) $$E = \left\{ (\alpha_C e_C a_C)^{\frac{\sigma_a - 1}{\sigma_a}} + (\alpha_M e_M a_M)^{\frac{\sigma_a - 1}{\sigma_a}} + (\alpha_P e_P a_P)^{\frac{\sigma_a - 1}{\sigma_a}} \right\}^{\frac{\sigma_a}{\sigma_a - 1}} \bar{n}^{INF}$$

(3.4d) $$e_C = 1 - \bar{n}_C^{INF} / \bar{n}^{INF}, \quad e_M = 1 - (\bar{n}_M^{INF} + \bar{n}_C^{INF}) / \bar{n}^{INF}, \quad e_P = 1 - (\bar{n}_P^{INF} + \bar{n}_C^{INF}) / \bar{n}^{INF}$$

n_i^{INF} is the probability that the agent will be infected with strain i on day t, where $\bar{n}^{INF} = \Sigma_i n_i^{INF}$.

In (3.4a) the term in square parentheses is daily utility from general consumption x and a composite good of effective drug treatments E; σ_u is the substitution elasticity between x and E, which governs the responsiveness of aggregate drug use to the ACT subsidy. α^{COST} / u_x is the monetized cost per day of infection (averaged over symptomatic and nonsymptomatic cases); in (3.4b) it is equal to the daily morbidity cost k plus the product of the mortality rate and the value of life v.

In (3.4c), E is a CES function over the infections treated by the three drugs, weighted by their respective effectiveness. The substitution elasticity σ_a governs the crowding-out effect of increased ACT use on the monotherapies, while α_C, α_M and α_P are distribution parameters chosen to imply an initial drug

[10] h_i is related to the "entomological inoculation rate" (EIR), a familiar concept in epidemiological literature, as follows: $h_i = b_2$EIR. That is, the EIR is the rate at which humans are bitten by mosquitoes potentially carrying a parasite, while h_i is the rate at which humans actually become infected.

mix and overall coverage rate. Finally, in (3.4d) drug effectiveness is the fraction of the infected population that is not resistant to that drug.

From duality theory, we can obtain the demand functions (see Appendix):

(3.5a) $$a_i = \frac{(p_i^{-\sigma_a}/(\alpha_i e_i)^{1-\sigma_a})E}{\bar{n}^{INF}\left[\Sigma_j (p_j/(\alpha_j e_j))^{1-\sigma_a}\right]^{\frac{\sigma_a}{1-\sigma_a}}}, \qquad p_E = \left\{\Sigma_j (p_j/(\alpha_j e_j))^{1-\sigma_a}\right\}^{\frac{1}{1-\sigma_a}}$$

(3.5b) $$E = \frac{\bar{n}^{INF} p_E^{-\sigma_n} \cdot INC}{1 + p_E^{1-\sigma_u}}, \qquad x = \frac{INC}{1 + p_E^{1-\sigma_u}}$$

where $i, j = M, P, C$; p_C is the net of subsidy price of ACT; and p_E is the unit cost of the composite. Partially differentiating the demand for ACT with respect to p_C yields:

(3.6a) $$\eta_{CC} = \frac{\partial a_C}{\partial p_C}\frac{p_C}{a_C} = \eta_{CC}^{cond} + \eta_{EE}\frac{p_C a_C}{\Sigma_j p_j a_j}$$

(3.6b) $$\eta_{CC}^{cond} = -\sigma_a\left\{1 + \frac{(p_C/(\alpha_C e_C))^{1-\sigma_a}}{\Sigma_j (p_j/(\alpha_j e_j))^{1-\sigma_a}}\right\}, \qquad \eta_{EE} = \frac{-(\sigma_u + p_E^{1-\sigma_u})}{1 + p_E^{1-\sigma_u}}$$

Equation (3.6a) decomposes the own-price elasticity for ACT, η_{CC} <0, into (a) the conditional elasticity η_{CC}^{cond} holding E fixed, which reflects inter-drug substitution; and (b) the own price elasticity for drugs as a whole, η_{EE} , times the share of spending on ACT in total drug spending.

3.3. Model Solution

An initial steady state with no drug use and only wild-type infections is obtained. We then solve the model with drug use and a given ACT subsidy (fixed over the planning period) using (3.2)–(3.5) and day-one population subgroups given by the no-drug steady state; our planning horizon is 20 years, so $\bar{t}$ = 20 × 365 periods.

To interpret welfare effects, we define the marginal cost (*MC*) and marginal external benefit (*MEB*) from increasing the subsidy as follows:

(3.7a) $$MC = s\int_0^{\bar{t}} e^{-\theta t}\left\{\frac{da_C}{ds} - \mu\left(a_C + s\frac{da_C}{ds}\right)\right\}N^{INF}\,dt$$

(3.7b) $$MEB = -\alpha^{COST}/u_x\int_0^{\bar{t}} e^{-\theta t}\frac{dN_{NET}^{INF}}{ds}dt, \quad -\frac{dN_{NET}^{INF}}{ds} = -\frac{dN^{INF}}{ds} + \Sigma_i e_i\frac{da_i}{ds}\rho^{TR}N^{INF}$$

MC is analogous to the (gross of externality) welfare effect in (2.4), discounted over the planning period. *MEB* is the marginal net reduction in infections, $-dN_{NET}^{INF}/ds$, discounted over the planning horizon, and

multiplied by the daily illness cost, where $-dN_{NET}^{INF}/ds$ is the overall reduction in infections, net of those due to increased drug treatment that are internal to drug users. $MEB > 0$ to the extent that the subsidy reduces the instantaneous transmission rate and increases average future drug effectiveness; the numerical model is unable to separately decompose the transmission and resistance externalities because of interaction between them.[11]

3.4. Parameter Values

We now discuss the baseline parameters and alternative values for transmission rates, resistance evolution, and drug-demand elasticities that are used for our main results; other parameters are varied in additional sensitivity analyses.

Entomological parameters. Aside from mosquito density, we take standard values for these parameters from the literature (Anderson and May, 1991).[12] We assume the mosquito mortality rate δ^{mos} = 1/10; the daily biting rate ρ = 0.3; the transmission efficiency from infected humans to mosquitoes, and vice versa, b_1 = 0.5 and b_2 = 0.8; and an incubation period of parasites in the mosquito of τ = 10 days. Mosquito density varies dramatically across sub-Saharan Africa with climate, the extent of urbanization and irrigation, and other factors; we consider values for m from 0.01 to 0.73, which imply an initial steady-state transmission rate for the wild-type infection of $h_W(0)$ = 0.004 to 0.300, or about 1.5 to 110 infectious bites per year, this is consistent with evidence noted below.[13]

Spontaneous recovery rates. Estimates of the time required to fully clear all infectious malaria parasites from the blood without treatment range from approximately 50 to several hundred days (Dietz et al., 1974; Gu et al., 2003; Sama et al., 2004);[14] for the baseline, we assume $\rho_W^{SP} = b_2/165$ from Smith et al. (2005). Based on previous data (Hayward et al., 2005) and evidence in field studies (e.g., Hastings and Donnelly, 2005; Koella, 1998), we assume spontaneous recovery rates are 20 percent and 45 percent

[11] That is, greater resistance leads to lower drug effectiveness, which lowers the transmission externality benefits from future drug use.

[12] These parameters have been obtained in various ways; for example, by analyzing samples of mosquitoes trapped in homes or using human volunteers as baits.

[13] Even higher biting rates are possible (Hay et al. 2005), though our results below converge as the biting rate approaches 100 per year.

[14] Measurement is confounded by the possibility of reinfection from additional bites prior to recovery and the possible persistence of parasites in the bloodstream at undetectable levels (e.g., Gu et al., 2003).

faster for strains resistant to monotherapies and ACT, respectively, $\rho_M^{SP} = \rho_P^{SP} = 1.2\,\rho_W^{SP}$, $\rho_C^{SP} = 1.45\,\rho_W^{SP}$.

Rate of immunity loss. Although a complete understanding of how immunity to malaria arises and persists following spontaneous recovery is still lacking, it is widely accepted that further infectious bites prolong immunity (e.g., Anderson and May, 1991; Aron and May, 1982; Hastings, 1997). We adopt the following, standard relation from the literature (e.g., Aron and May, 1982): $\gamma = h/(e^{hT} - 1)$, where *T* is immunity duration without additional biting, assumed to be 100 days. At low transmission rates, immunity lasts about 200 to 300 days, but at very high transmission rates it can last for years.

Mortality rates. Roll Back Malaria et al. (2005, Annex 1) and the United Nations Statistics Division (2006) estimate that malaria kills between 0.001 and 0.300 percent of those who are infected each year; we take a value for our baseline of δ^{INF} = 0.0015/365. Based on the same sources, we assume an average life expectancy of 45 years, or δ^{N} = 1/(45×365).

Steady state with no drug use. Figure 2 plots the initial steady-state population subgroups with no drug use against the transmission rate (given other baseline parameters). The proportion of the population that is either infected (whether symptomatic or not) or immune on a given day, termed the "parasite rate," varies from near 0 to 96 percent as the transmission rate increases.[15] The infected class peaks at 58 percent and then declines beyond a rate of 11 infectious bites per year, because a higher biting rate lowers γ and increases the size of the immune population at the expense of the infected population (Snow and Marsh, 2002). We illustrate "low," "baseline," "high," and "extreme" scenarios corresponding to about 1.5, 7.5, 15, and 110 infectious bites per year, respectively. Initial infection rates for these scenarios are 0.30, 0.57, 0.57, and 0.06, respectively, the latter two rates being beyond the peak of the infection curve.

Initial drug use and treatment recovery rate. Only a small fraction of those with infections are symptomatic. Assuming that a wild-type infection is symptomatic for 5 days (Chima et al., 2003) and multiplying by ρ_W^{SP}, 5 of 200 infected individuals are symptomatic on a given day. Further, only a

[15] This broad range is consistent with available evidence. For example, Mbogo et al. (2003) estimated parasite rates of 38 to 83 percent in different regions with different rainfall levels in Eastern Kenya; Beier et al. (1999) found rates of 0 to 90 percent across 31 sites in Africa; Hay et al. (2005) found rates of 0 to almost 100 percent depending on the terrain in Africa; Wang et al. (2006) estimated rates of 26 percent among health center patients in urban Ivory Coast; and Mendis et al. (2000) found rates of 33 to 63 percent in rural Mozambique.

fraction of these individuals take drugs because of their cost or unavailability (others use "self therapy"). Based on previous data (Branch et al., 2005) we assume that, in the absence of an ACT subsidy, 20 percent of symptomatic individuals receive antimalarial treatment. Therefore, infected individuals are initially treated once every 200 days or, normalizing $\rho^{TR} = 1$ (individuals stop being infectious after one treatment day), $a(0) = 0.005$. On the basis of conversations with experts at Roll Back Malaria, we assume that 4, 15 and 1 percent of symptomatic infections are treated with AMT, PMT, and ACT, respectively; all drugs initially have 100 percent effectiveness.

Resistance evolution. The probability that spontaneous resistance will emerge to a new drug is very difficult to gauge *ex ante*.[16] For example, despite hundreds of millions of treatments, spontaneous resistance to chloroquine apparently occurred only a few times (Wootton et al., 2002), suggesting an r value of approximately 10^{-9} for that drug, whereas resistance may arise in as many as one of every three patients taking atovaquone monotherapy (White and Pongtavornpinyo 2003). It is believed that the likelihood of spontaneous resistance to artemisinin is much lower than for other antimalarials, since it kills parasites much faster and is quickly eliminated from the body (White 1998). We illustrate low, baseline, and high values for r_P of 10^{-8}, 10^{-5} and 10^{-3} and for r_M of 10^{-10}, 10^{-8} and 10^{-5}, respectively; resistance evolution for ACT is the product of the rate for its constituent drugs, $r_C = r_P r_M$ (White, 1999; White and Pongtavornpinyo, 2003; White, 2004).[17]

Drug prices. Based on WHO (2003, 25) and Médecins Sans Frontières (2003, 17, 20), we set producer prices at $0.30, $1.00, and $1.30 for PMT, AMT, and ACT, respectively. In practice, the producer price of ACT may decline in the future if synthetic drugs are developed; we consider other assumptions in the sensitivity analysis.

Demand response parameters. No econometric evidence on drug-demand elasticities is available for sub-Saharan Africa; we therefore consider a plausible range of possibilities. The greater σ_a becomes, the greater the effect of ACT subsidies on crowding out monotherapies; we calibrate σ_a such that demand for

[16] Malaria parasites are highly complex and have an extremely high rate of genetic variability (Kidgell et al. 2006). In most malarial infections, resistant mutants represent a tiny fraction of all parasites, and they rarely become dominant unless the host receives drug treatment.

[17] In practice, individuals may stop drug consumption without completing the treatment course, or mistakenly take antimalarials for a non-malaria infection. In either case, the emergence of resistant parasites could be increased, though the evidence on this is weak (White and Pongtavornpinyo 2003). In any case, these possibilities are implicitly taken into account in our choice of the r_is, since they are crudely based on prior experience with resistance evolution.

ACT would be 40, 70, and 100 percent of that for PMT (prior to resistance evolution) if the consumer price of ACT is lowered to that of PMT.[18] The greater σ_u becomes, the greater the effect of subsidies on increasing overall drug use and reducing infection transmission; we calibrate σ_u to imply that total drug coverage would rise from 20 percent to 27.5, 35, or 45 percent, respectively (prior to resistance evolution) if the price of ACT were half that for PMT. [19] Combining these cases leads to a low elasticity scenario where $\sigma_u = 0.72$, $\sigma_a = 1.22$ ($\eta_{CC} = -1.45$, $\eta_{EE} = -0.49$); a baseline scenario with $\sigma_u = 0.85$, $\sigma_a = 1.62$ ($\eta_{CC} = -1.93$, $\eta_{EE} = -0.85$); and a high scenario with $\sigma_u = 1.05$, $\sigma_a = 1.85$ ($\eta_{CC} = -2.23$, $\eta_{EE} = -1.05$).

Figure 3 shows how drug demand responds to the ACT subsidy in the baseline case (prior to resistance evolution). The subsidy initially increases ACT use at the expense of other drugs; only beyond a subsidy of approximately \$0.80 (when the price of ACT approaches that of PMT) does overall drug use start to noticeably increase. We do not consider subsidies much in excess of \$1, since demand becomes unstable under CES preferences, as prices tend to zero (or *s* tends to \$1.30).

Cost of illness. Direct morbidity costs (e.g., drugs, clinic and physician costs, access costs) are estimated at around \$0.40 to \$4.00 per episode of symptomatic malaria in sub-Saharan Africa, or \$0.08 to \$0.80 per day of illness, while indirect costs (time lost from incapacitation or caring for sick children) are estimated at around \$0.15 to \$4.50 per day of symptomatic illness (Chima et al. 2003). We assume morbidity costs are \$2.5 per day (or \$12.5 per episode); multiplying by the fraction of symptomatic infections gives k = 6.3 cents. To value mortality effects, we assume a value of life v = \$50,000, based on (and updating) extrapolations across different countries (Miller, 2000, Table 5). Combining morbidity and mortality components gives the cost per day of illness u^{COST}/u_x = 26.8 cents.

Discount rate and altruism parameter. We start with an annual discount rate of 3 percent ($\theta = 0.03/365$), which is commonly used to evaluate health policy interventions in developing countries (Drummond et al. 1997). For the benchmark case we assume no altruistic benefits to donors (i.e., $\mu = 0$ or the cost of financing \$1 of subsidy is \$1); this assumption is relaxed later.

[18] If anything, demand for ACT would likely be lower than for PMT at equal prices because of consumer unfamiliarity with ACT, and a less well-developed distribution network for ACT.

[19] We cannot consider values for σ_u much below these cases because agents would compensate for a general decline in drug effectiveness by consuming more drugs, which causes instability (in practice, individuals and institutions would likely rely more on self-therapy and other remedies as drug effectiveness falls).

4. Simulation Results

We now discuss drug effectiveness, infection rates, and welfare effects of ACT subsidies under alternative scenarios for transmission rates, drug-demand responses, resistance evolution, and the cost of illness. We then provide additional sensitivity analyses, including the implications of altruistic donors.

4.1. Drug Effectiveness and Infection Rates

Figure 4(a) shows the effectiveness of individual drugs over time and the average drug effectiveness (weighted by drug share) under baseline parameters and drug use (with no ACT subsidy). For each drug, effectiveness is initially unity then declines sharply as resistance evolves exponentially; drug use also falls at this point (Boni and Feldman, 2005). This decline occurs after about 4 years for PMT, reflecting its relatively high use and resistance evolution rate, and after about 12 and 14 years for AMT and ACT, respectively. Long-run effectiveness for PMT is lowest, at 0.12, reflecting its higher use and the lower spontaneous recovery rate from the PMT-resistant strain, while effectiveness for ACT and AMT stabilizes at about 0.45 and 0.35, respectively. Average drug effectiveness drops to about 0.6 when PMT fails, and then to about 0.25 when AMT and ACT fail.

Figure 4(b) shows average drug effectiveness for other drug use scenarios (and baseline parameters): one in which all drug use is scaled up in proportion so that initial total coverage for symptomatic infections is 50 percent, and another in which total initial drug coverage stays at 20 percent but ACT is half of drug use (monotherapies are scaled back in equal proportion). With more intensive overall drug use, all drugs fail much sooner than in the baseline case, and average long-run drug effectiveness is much lower. With a greater ACT share, PMT fails later than in the baseline, while ACT and AMT fail a little quicker; average drug effectiveness is greater than in the baseline for the first 12 years, though dips below it thereafter.

In Figure 4(c) we vary the initial transmission rate given baseline parameters and drug use. Here the infected population and drug use are smaller than in the baseline case for the low and extreme transmission scenarios (see above), hence drug effectiveness lasts longer. There is little difference in effectiveness between the baseline and high transmission rate case, given that the initial infection rate and drug use are about the same. Finally, Figure 4(d) shows that the average drug effectiveness falls somewhat slower or faster with the low or high rates of resistance evolution, respectively.

Figure 5 illustrates the reduction in infection rate over time (relative to the steady state with no drug use) for baseline parameters. With baseline drug demand, the infection rate is initially reduced by about 0.08 (the infected population share is about 0.48 compared with 0.56 in the no-drug steady state). This difference falls to 0.04 when PMT fails, though it increases slightly when ACT fails as people recover faster spontaneously from ACT-resistant strains. If initial total drug coverage is scaled up to 50

percent, the reduction in infections over time is more substantial, while if ACT accounts for half of an initial 20 percent drug coverage, the reduction in infections is also higher (after three years) because of the more intensive use of the most effective drug. Qualitatively similar results (not shown in the figure) apply at different transmission rates.[20]

4.2. Welfare Effects of ACT Subsidies

In Figure 6 we plot the marginal social cost and marginal external benefit from increasing the subsidy (discounted over 20 years), according to (3.7), in dollars per capita and under baseline parameters. The marginal cost is increasing because the difference between the marginal supply cost and the marginal private benefit to ACT consumers is widening, and successive incremental increases in the subsidy cause progressively higher increases in drug demand, given the convex demand curve. The marginal external benefit is also rising because the marginal impact on reducing infection transmission and/or resistance evolution is rising (again because of convex demand) and exceeds the marginal cost up to a subsidy of $1.18. Integrating between the MEB and MC curves, the total (discounted) welfare gain from a $1 subsidy is $25 per capita; the benefit-cost ratio is about 6:1.

Figure 7(a) show how total welfare gains from a $1 subsidy vary with the initial transmission rate and drug-demand elasticities (given other baseline parameters). Welfare gains initially rise with the transmission rate (and drug use) but then decline beyond about 1.5 infectious bites per year and become (slightly) negative beyond about 60 to 80 infectious bites per year. At high biting rates, externality benefits from both more drug use and longer drug effectiveness are greatly diminished, since treated individuals are quickly reinfected. Figure 7(b) shows how welfare gains from the $1 subsidy vary with the cost of illness (for different drug-demand elasticities and baseline values for other parameters); welfare gains are still positive at $3 to $8, even if the cost of illness is one-third that assumed in our baseline. In these two panels, the benefit-cost ratio is at least 2:1 when infectious bites per year are below about 45 and the daily cost of illness is above about $0.10.

Finally, Table 1 shows how welfare gains vary with resistance evolution rates for AMT and PMT (and therefore also ACT) for selected transmission and demand response scenarios. We consider cases where rates are scaled up and down for AMT and PMT simultaneously and one at a time (given the baseline rate for the other drug). The main point here is that welfare gains are only moderately affected so even though resistance evolution rates are highly uncertain, the efficiency case for ACT subsidies is still robust. (These results do not necessarily imply that resistance is unimportant because the effect is

[20] Even for transmission rates beyond the peak of the infection curve in Figure 2, drug use still reduces the infection rate, though the effect is small.

confounded in Table 1; faster resistance strengthens efficiency gains from crowding out monotherapies but lowers (future) efficiency gains from reduced infection transmission as drugs fail faster).

4.3. Further Sensitivity Analysis

The first part of Table 2 indicates how welfare effects from the $1 ACT subsidy increase as we allow for altruistic benefits to donors; these benefits reduce the net cost of financing the subsidy. Aside from the low transmission rate case, relative welfare gains rise rapidly. For example, if altruistic benefits are $0.30 per $1 of subsidy outlays, welfare gains are three to four times as high as they are with no altruism in the baseline and high transmission rate scenarios. Varying the producer price of ACT (keeping the subsidized consumer price at $0.30), spontaneous recovery rates and rates of immunity loss generally have only a modest impact on welfare gains.

5. Conclusion

Our results suggest that large subsidies to lower the price of artemisinin combination treatments (ACTs) so that they are comparable to prices of alternative antimalarial drugs in sub-Saharan Africa are warranted on externality grounds across many scenarios for epidemiological and economic parameters. This outcome is due to large efficiency gains from the effect of the subsidy on deterring use of alternative drugs for which resistance evolves faster, and by lowering infection transmission rates through expanding overall drug coverage. However, at extremely high infection transmission rates (in excess of about 60 to 80 infectious bites per year), subsidies may not be efficient because recovering individuals quickly become reinfected and thus there is little impact on reducing the size of the infected population.

This analysis might be extended in future work to study a broader range of malarial policy interventions, such as subsidies for insecticide-treated bed nets and indoor residual spraying. It would be especially useful to analyze, for a given total budget provided by external donors, the optimal balance between spending on such prevention measures, and spending on drug treatments, and to what extent this trade-off might critically hinge on the epidemiological and economic parameters discussed above, particularly the infection transmission rate. More generally, the type of framework developed here might be extended to analyze policy interventions in the context of other infectious diseases, such as HIV/AIDS and tuberculosis.

References

Anderson, R.M. and R.M. May (1991). *Infectious Diseases of Humans*. Oxford: Oxford University Press.

Aron, J. and R.M. May (1982). "The Population Dynamics of Malaria." In R.M. Anderson (ed.), *Population Dynamics and Infectious Disease*. London: Chapman and Hall: 139–79.

Arrow, K.J., C.B. Panosian, et al., eds. (2004). *Saving Lives, Buying Time: Economics of Malaria Drugs in an Age of Resistance*. Board on Global Health. Washington DC: Institute of Medicine.

Atkinson, A.B. (2005). *New Sources of Development Finance*. Oxford: Oxford University Press.

Beier, J., G. Killeen, et al. (1999). "Short Report: Entomologic Inoculation Rates and Plasmodium Falciparum Malaria Prevalence in Africa." *American Journal of Tropical Medicine and Hygiene* **61**(1): 109–13.

Bonhoeffer, S., M. Lipsitch, et al. (1997). "Evaluating Treatment Protocols to Prevent Antibiotic Resistance." *Proceedings of the National Academy of Sciences of the United States of America* **94**(22): 12106–11.

Boni, M.F. and M.W. Feldman (2005). "Evolution of Antibiotic Resistance by Human and Bacterial Niche Construction." *Evolution: International Journal of Organic Evolution* **59**(3): 477–91.

Branch, O., W.M. Casapia, et al. (2005). "Clustered Local Transmission and Asymptomatic Plasmodium Falciparum and Plasmodium Vivax Malaria Infections in a Recently Emerged, Hypoendemic Peruvian Amazon Community." *Malaria Journal* **4**: 27.

Chima, R.I., C.A. Goodman, et al. (2003). "The Economic Impact of Malaria in Africa: A Critical Review of the Evidence." *Health Policy* **63**(1): 17–36.

Cornille-Brogger, R., H.M. Mathews, et al. (1978). "Changing Patterns in the Humoral Immune Response to Malaria before, during, and after the Application of Control Measures: A Longitudinal Study in the West African Savanna." *Bulletin of the World Health Organization* **56**(4): 579–600.

Dietz, K., L. Molineaux, et al. (1974). "A Malaria Model Tested in the African Savannah." *Bulletin of the World Health Organization* **50**(3–4): 347–57.

Drummond, M., B. O'Brien, et al. (1997). *Methods for the Economic Evaluation of Health Care Programmes (second edition)*. Oxford: Oxford University Press.

Greenwood, B.M. (1987). "Asymptomatic Malaria Infections—Do They Matter?" *Parasitology Today* **3**(7): 206–14.

Gu, W., C.M. Mbogo, et al. (2003). "Low Recovery Rates Stabilize Malaria Endemicity in Areas of Low Transmission in Coastal Kenya." *Acta Tropica* **86**(1): 71–81.

Hastings, I.M. (1997). "A Model for the Origins and Spread of Drug-Resistant Malaria." *Parasitology* **115**: 133–41.

Hastings, I.M. and M.J. Donnelly (2005). "The Impact of Antimalarial Drug Resistance Mutations on Parasite Fitness, and Its Implications for the Evolution of Resistance." *Drug Resistance Updates* **8**(1–2): 43–50.

Hay, S.I., C.A. Guerra, et al. (2005). "Urbanization, Malaria Transmission and Disease Burden in Africa." *Nature Reviews Microbiology* **3**(1): 81-90.

Hayward, R., K.J. Saliba, et al. (2005). "Pfmdr1 Mutations Associated with Chloroquine Resistance Incur a Fitness Cost in Plasmodium Falciparum." *Molecular Microbiology* **55**(4): 1285–95.

Hien, T.T., N.J. White, et al. (1993). "Qinghaosu." *The Lancet* **341**(8845): 603–608.

Jambou, R., E. Legrand, et al. (2005). "Resistance of Plasmodium Falciparum Field Isolates to in-Vitro Artemether and Point Mutations of the Serca-Type Pfatpase6." *The Lancet* **366**(9501): 1960–63.

Kidgell, C., S K. Volkman, et al. (2006). "A Systematic Map of Genetic Variation in Plasmodium Falciparum." *PLoS Pathogens* **2**(6): e57.

Koella, J. and R. Antia (2003). "Epidemiological Models for the Spread of Anti-Malarial Resistance." *Malaria Journal* **2**: 3.

Koella, J.C. (1998). "Costs and Benefits of Resistance against Antimalarial Drugs." *Parasitology Today* **14**(9): 360–64.

Laxminarayan, R. (2004). "Act Now or Later? Economics of Malaria Resistance." *American Journal of Tropical Medicine and Hygiene* **71**(2 Suppl): 187–95.

Mbogo, C.M., J.M. Mwangangi, et al. (2003). "Spatial and Temporal Heterogeneity of Anopheles Mosquitoes and Plasmodium Falciparum Transmission along the Kenyan Coast." *American Journal of Tropical Medicine and Hygiene* **68**(6): 734–42.

Mendis, C., J.L. Jacobsen, et al. (2000). "Anopheles Arabiensis and An. Funestus Are Equally Important Vectors of Malaria in Matola Coastal Suburb of Maputo, Southern Mozambique." *Medical and Veterinary Entomology* **14**(2): 171–80.

Miller, T.R. (2000). "Variations between Countries in Values of Statistical Life." *Journal of Transport Economics and Policy* **34**: 169–88.

Médecins Sans Frontières (2003). *Act Now to Get Malaria Treatment That Works to Africa*. Geneva: Médecins Sans Frontières.

Philipson, T.J. and S. Mechoulan (2003). "Intellectual Property and External Consumption Effects: Generalizations from Health Care Markets." Working Paper 9598. Cambridge, MA: National Bureau of Economic Research.

Pringle, G. and S. Avery-Jones (1966). "Observations on the Early Course of Untreated Falciparum Malaria in Semi-Immune African Children Following a Short Period of Protection." *Bulletin of the World Health Organization* **34**(2): 269–72.

Roll Back Malaria, World Health Organization, UNICEF (2005). *World Malaria Report 2005*. Geneva: WHO, 2005.

Rudholm, N. (2002). "Economic Implications of Antibiotic Resistance in a Global Economy." *Journal of Health Economics* **21**: 1071–83.

Sama, W., G. Killeen, et al. (2004). "Estimating the Duration of Plasmodium Falciparum Infection from Trials of Indoor Residual Spraying." *American Journal of Tropical Medicine and Hygiene* **70**(6): 625–34.

Smith, D.L., J. Dushoff, et al. (2005). "The Entomological Inoculation Rate and Plasmodium Falciparum Infection in African Children." *Nature* **438**(7067): 492–95.

Smith, D.L. and F.E. McKenzie (2004). "Statics and Dynamics of Malaria Infection in Anopheles Mosquitoes." *Malaria Journal* **3**: 13.

Snow, R.W., C.A. Guerra, et al. (2005). "The Global Distribution of Clinical Episodes of Plasmodium Falciparum Malaria." **434**(7030): 214–217.

Snow, R.W. and K. Marsh (2002). "The Consequences of Reducing Transmission of Plasmodium Falciparum in Africa." *Advances in Parasitology* **52**: 235–64.

Trape, J.F. (2001). "The Public Health Impact of Chloroquine Resistance in Africa." *American Journal of Tropical Medicine and Hygiene* **64**(1–2 Suppl): 12–17.

Trape, J.F., G. Pison, et al. (1998). "Impact of Chloroquine Resistance on Malaria Mortality." *Comptes Rendus de l'Académie des Sciences. Série III, Sciences de la vie* **321**(8): 689–97.

United Nations Statistics Division (2006). *Common Database* Accessed 2006-05-31, available at http://unstats.un.org.

Wang, S.J., C. Lengeler, et al. (2006). "Rapid Urban Malaria Appraisal (Ruma) III:Epidemiology of Urban Malaria in the Municipality of Yopougon (Abidjan)." *Malaria Journal* **5**(1): 28.

White, N. (1999). "Antimalarial Drug Resistance and Combination Chemotherapy." *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* **354**(1384): 739–49.

White, N.J. (1998). "Preventing Antimalarial Drug Resistance through Combinations." *Drug Resistance Updates* **1**: 3–9.

White, N.J. (2004). "Antimalarial Drug Resistance." *Journal of Clinical Investigation* **113**(8): 1084–92.

White, N.J. and W. Pongtavornpinyo (2003). "The De Novo Selection of Drug-Resistant Malaria Parasites." *Proceedings Biological Sciences* **270**(1514): 545–54.

WHO (2001). *Antimalarial Drug Combination Therapy. Report of a WHO Technical Consultation*. Geneva: World Health Organization.

WHO (2003). *Improving the Affordability and Financing of Artemisinin-Based Combination Therapies*. Geneva: World Health Organization.

Wootton, J.C., X. Feng, et al. (2002). "Genetic Diversity and Chloroquine Selective Sweeps in Plasmodium Falciparum." *Nature* **418**(6895): 320–23.

Appendix

Derivation of Equation (2.4)

The welfare effect of an incremental increase in *s* is obtained by first solving the household optimization problem to obtain the indirect utility function and then totally differentiating the indirect utility function with respect to *s*.

(i) Household optimization. Using (2.1) and (2.2) this is given by:

(A1) $$V\{s,\bar{e}_C,\bar{e}_M,\bar{n}^{INF}\} = \underbrace{Max}_{x,a_C,a_M}\ u\{\bar{n}^{INF},x,E[\bar{e}A_C,\bar{e}A_M]\} + \lambda[INC-(p_C-s)A_C-p_M A_M-p_x x]$$

where $V\{.\}$ is the indirect utility function. Households choose x, A_C and A_M to maximize utility subject to the budget constraint, taking resistance or drug effectiveness, infection transmission, and government policy parameters as given. From the resulting first-order conditions and budget constraint we obtain the implicit demand functions $y\{s,\bar{e}_C,\bar{e}_M,\bar{n}^{INF}\}$, where $y = a_C, a_M, x$ and substituting them into the utility function $u\{.\}$ yields the indirect utility function $V\{.\}$ defined in (A1).

Partially differentiating $V\{.\}$ gives:

(A2) $$\frac{\partial V}{\partial s}=\lambda A_C,\qquad \frac{\partial V}{\partial \bar{e}_i}=u_E\frac{\partial E}{\partial \bar{e}_i},\ i=C,M;\qquad \frac{\partial V}{\partial \bar{n}^{INF}}=u_{\bar{n}^{INF}}$$

(ii) Welfare effect of increasing s. Totally differentiating the indirect utility function with respect to *s* gives:

(A3) $$\frac{dV}{ds}=\frac{\partial V}{\partial s}+\frac{\partial V}{\partial \bar{e}_C}\frac{d\bar{e}_C}{ds}+\frac{\partial V}{\partial \bar{e}_M}\frac{d\bar{e}_M}{ds}+\frac{\partial V}{\partial n^{INF}}\frac{dn^{INF}}{ds}$$

From totally differentiating expressions in (2.1b) and (2.1c):

(A4) $$\frac{d\bar{e}_j}{ds}=\left\{\frac{\partial \bar{e}_j}{\partial A_C}\frac{dA_C}{ds}+\frac{\partial \bar{e}_j}{\partial A_M}\frac{dA_M}{ds}\right\}$$

(A5) $$\frac{dn^{INF}}{ds}=\sum_j\left(\frac{\partial n^{INF}}{\partial A_i}+\sum_j\frac{\partial n^{INF}}{\partial \bar{e}_j}\frac{\partial \bar{e}_j}{\partial A_i}\right)\frac{dA_i}{ds},\qquad i,j=C,M$$

Substituting (A4)-(A5) in (A3), subtracting the marginal cost of subsidy finance to donors, $dG/ds=(1-\mu)(A_C+sdA_C/ds)$, and collecting terms in dA_C/ds and dA_C/ds gives (2.4).

Deriving Equation (3.5)

Using duality theory, the first step in the household optimization is to choose consumption of individual drugs to minimize spending for a given amount of the composite good *E*. That is, households solve

(A7) $$C\{.\}=\underbrace{Min}_{a_C,a_M,a_P}\ p_C a_C+p_M a_M+p_P a_P$$

subject to $$E=\alpha_E\left\{(\alpha_C e_C a_C)^{\frac{\sigma_a-1}{\sigma_a}}+(\alpha_M e_M a_M)^{\frac{\sigma_a-1}{\sigma_a}}+(e_P a_P)^{\frac{\sigma_a-1}{\sigma_a}}\right\}^{\frac{\sigma_a}{\sigma_a-1}}\bar{n}^{INF}$$

where $C\{.\}$ denotes the cost function. Following standard derivations for CES functions (e.g., Varian 1984, Ch. 2), the cost function is:

$$\text{(A8)} \qquad C\{.\} = \left\{(p_M/(\alpha_M e_M))^{1-\sigma_a} + (p_C/(\alpha_C e_C))^{1-\sigma_a} + (p_P/(\alpha_P e_P))^{1-\sigma_a}\right\}^{\frac{1}{1-\sigma_a}} E/(\alpha_E \overline{n}^{INF})$$

Differentiating the cost function with respect to individual drug prices gives the conditional demand functions in (3.5a). The price of the composite good in (3.5a) is simply total spending on the composite $C\{.\}$ divided by quantity of the composite E.

The second step of the household optimization is to choose x and E to maximize the upper nest of the utility function subject to the budget constraint. From the individual's perspective, decisions taken at different points in time are independent, so we can solve the instantaneous maximization problem:

$$\text{(A9)} \qquad \underbrace{Max}_{x,E} \quad u = \left[x^{\frac{\sigma_u - 1}{\sigma_u}} + E^{\frac{\sigma_u - 1}{\sigma_u}}\right]^{\frac{\sigma_u}{\sigma_u - 1}} - \alpha^{COST}\overline{n}^{INF} \quad \text{subject to} \quad p_E E + p_x x = INC$$

Again, from standard derivations (Varian 1984, Ch. 2), the indirect utility function is given by:

$$\text{(A10)} \quad V = INC \cdot \{p_E^{1-\sigma_u} + 1\}^{\frac{1}{\sigma_u - 1}} - \alpha^{COST}\overline{n}^{INF}$$

The demand functions in (3.5b) are obtained by applying Roy's identity to (A10).

Figure 1. Welfare Effects from Increasing the ACT Subsidy

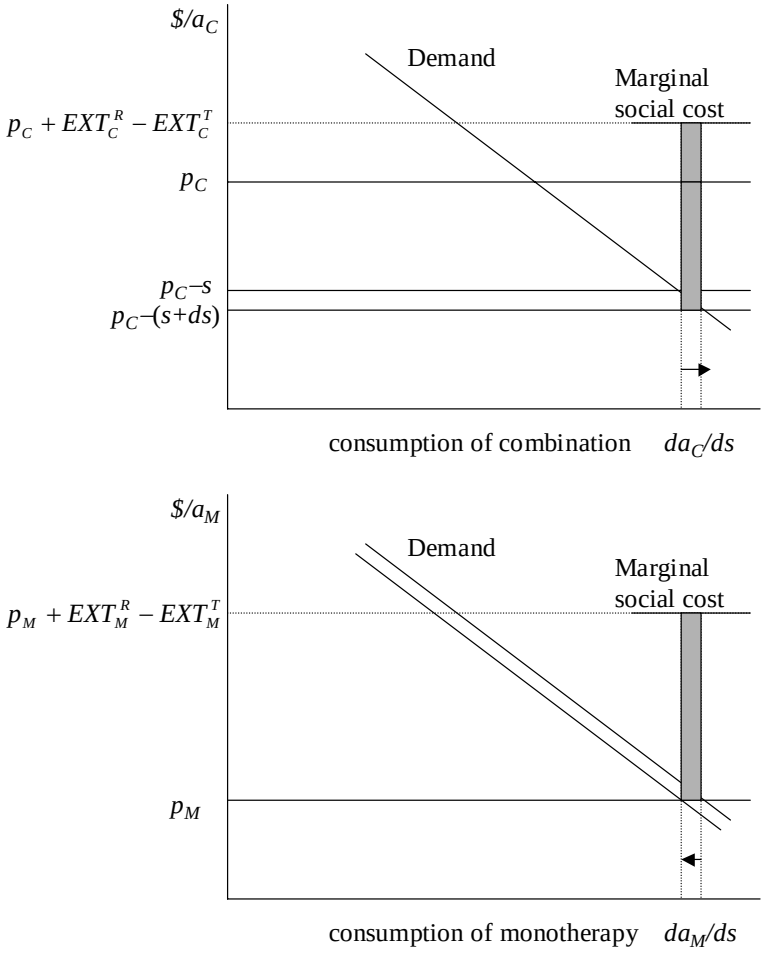


Figure 2. Population Subgroups in Initial Steady State with No Drug Use

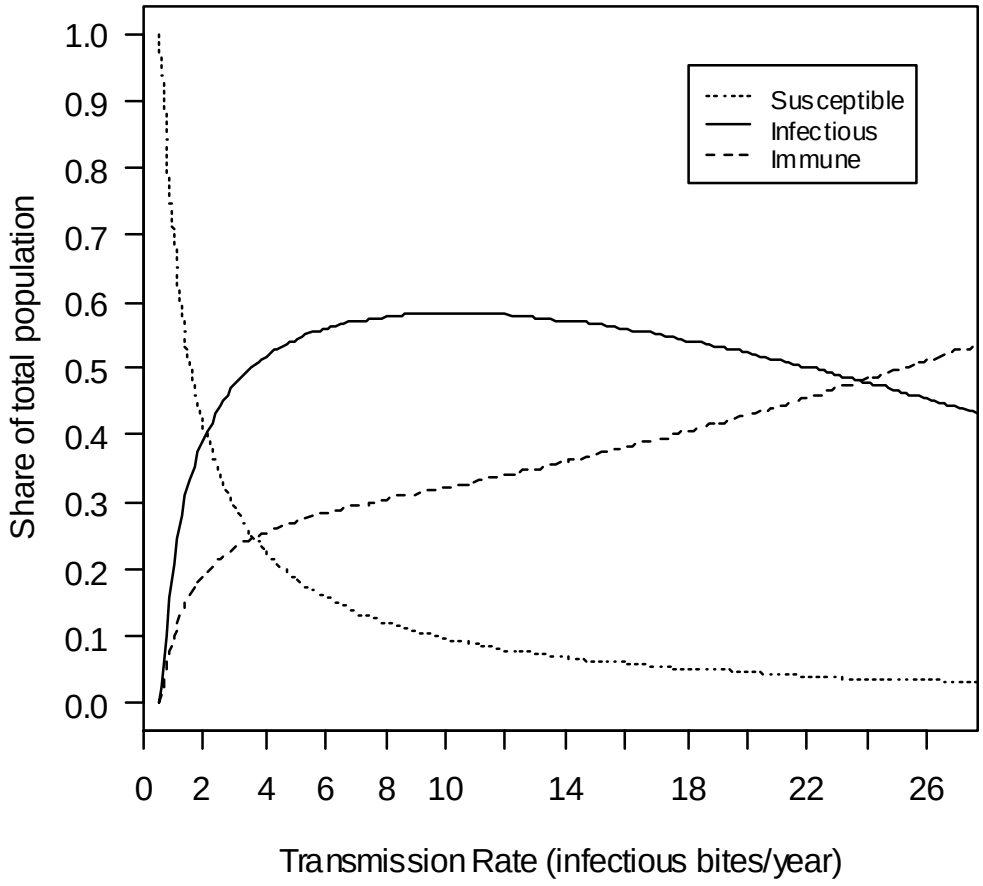


Figure 3. Initial Drug Coverage at Different Subsidy Levels

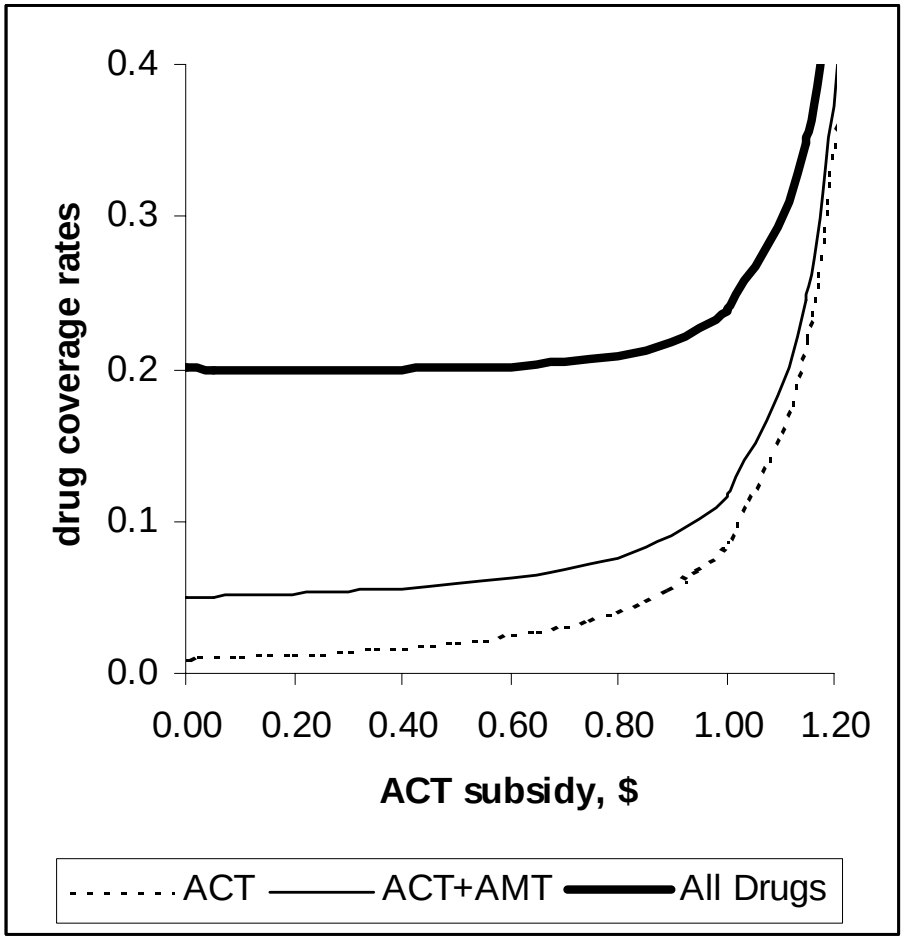
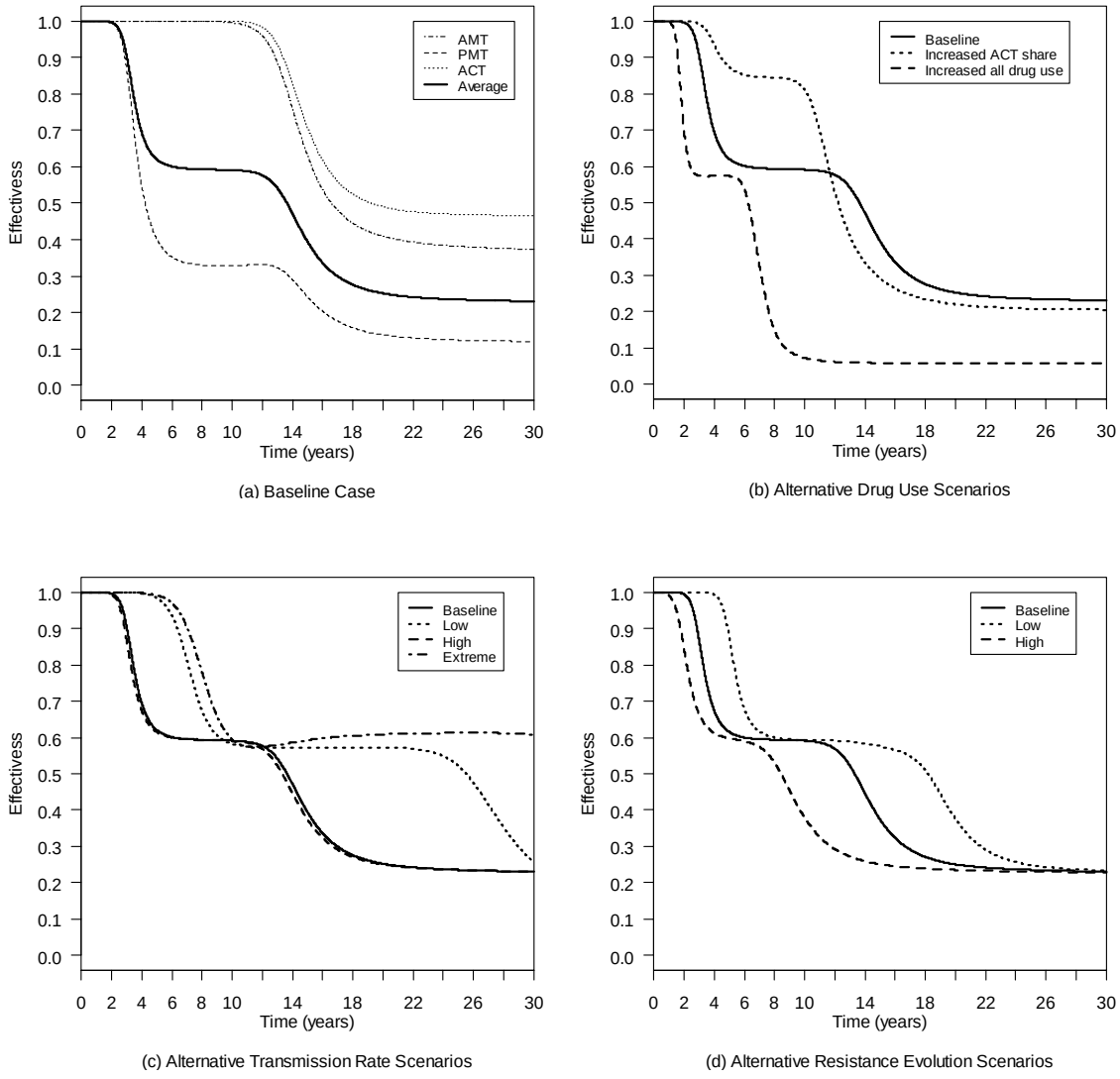


Figure 4: Drug Effectiveness over Time



(a) Baseline Case

(b) Alternative Drug Use Scenarios

(c) Alternative Transmission Rate Scenarios

(d) Alternative Resistance Evolution Scenarios

Figure 5: Impact of Drug Use on Reducing Infection Rate
(for baseline parameter values)

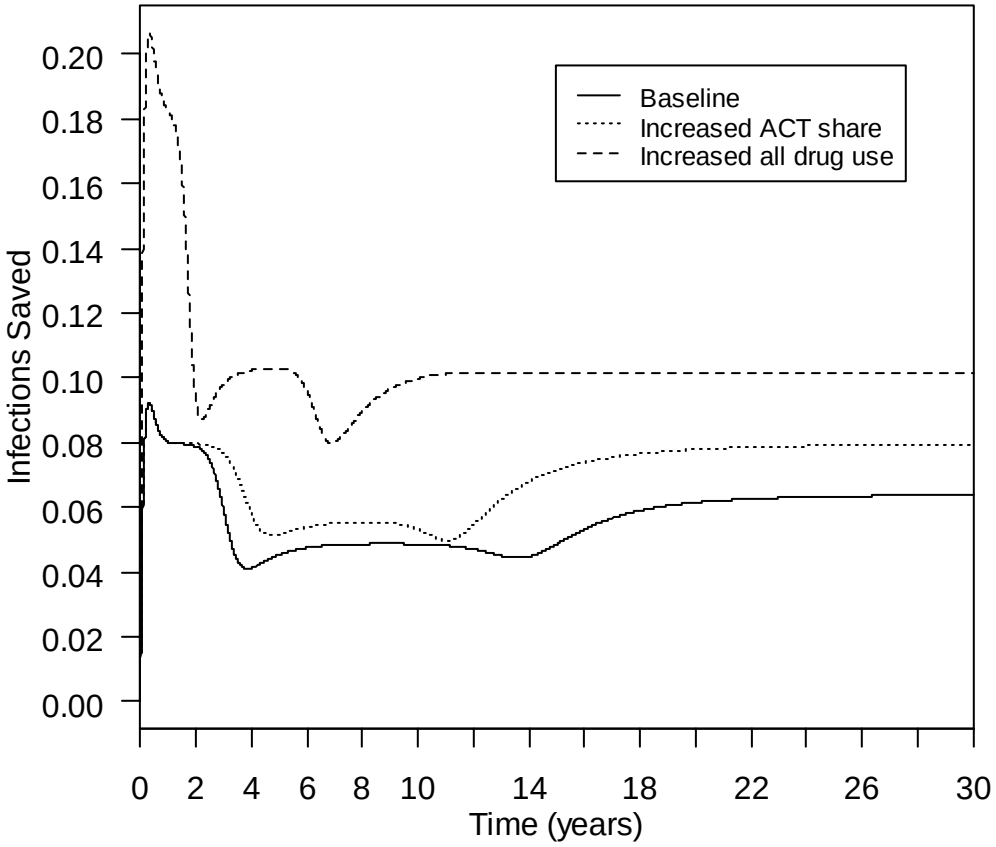


Figure 6: Marginal Cost and External Benefit from ACT Subsidy
(for baseline parameter values)

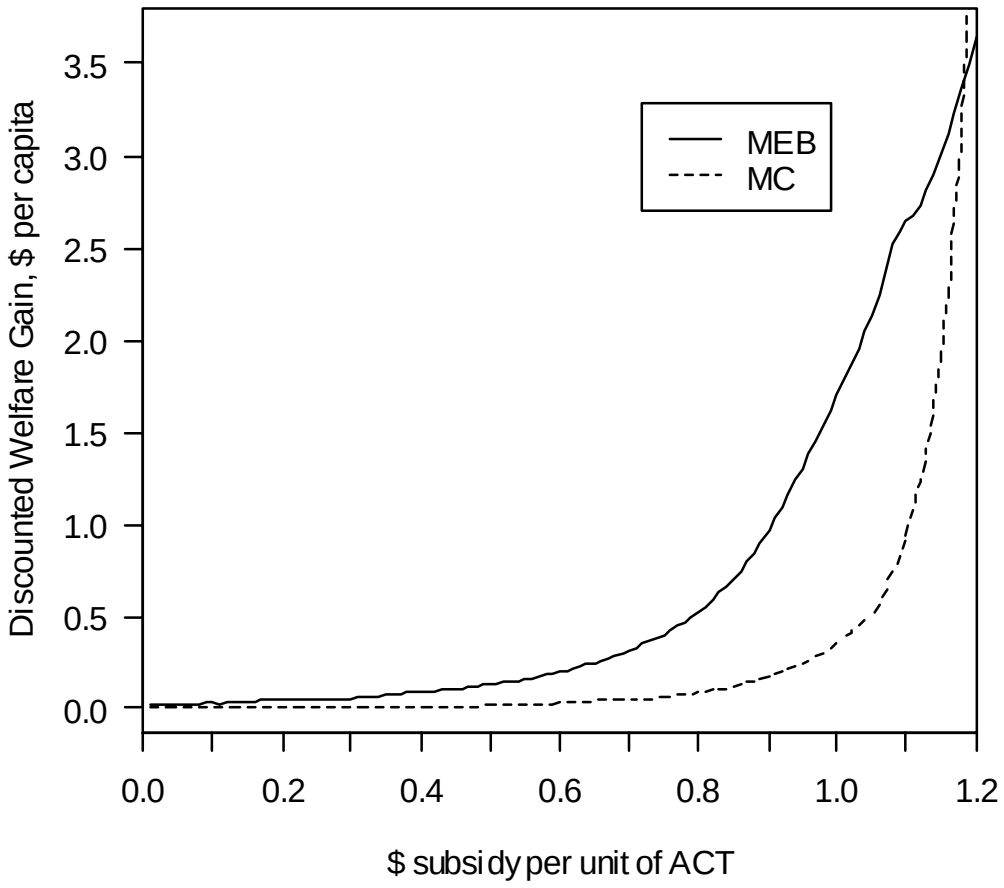
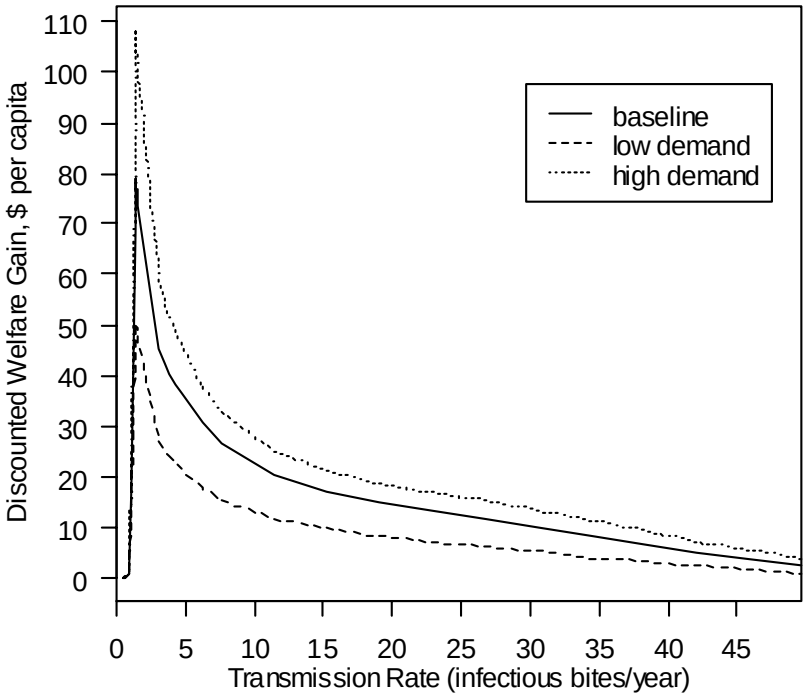
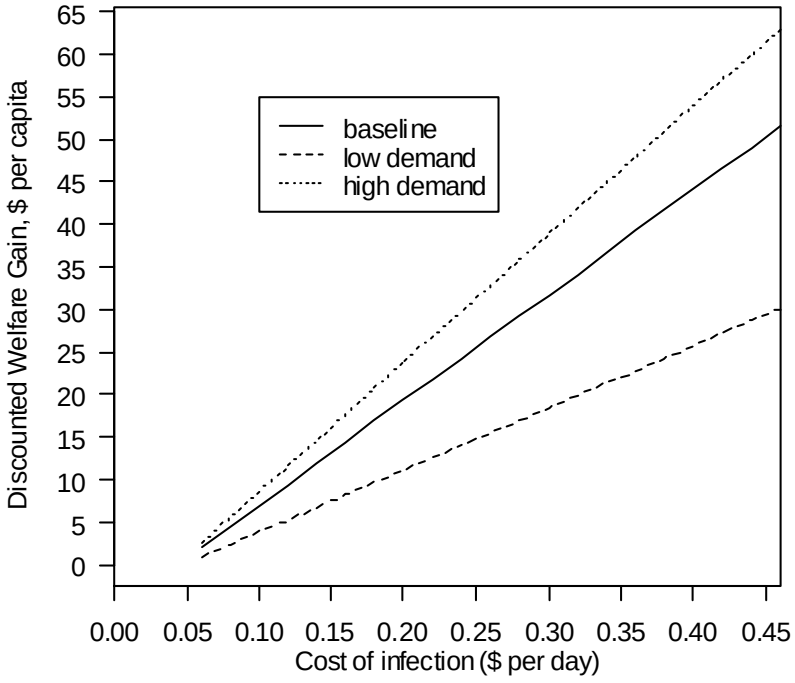


Figure 7: Welfare Gain from $1 Subsidy under Alternative Scenarios



(a) Alternate Transmission Rates



(b) Cost of Illness

Table 1. Welfare Gain from Reducing ACT Price to $0.30: Alternative Resistance Scenarios
(Discounted Welfare Gain, $ per capita)

	initial transmission rate						
	low			baseline		high	
Demand responses	low	high	low	baseline	high	low	high
Baseline case	47.3	99.3	15.4	26.8	32.7	9.6	21.1
All resistance rates							
high value	34.0	74.6	16.4	28.3	32.3	10.5	21.4
low value	41.7	103.2	14.3	23.8	31.3	8.8	19.6
AMT resistance rate							
high value	33.8	75.2	16.2	27.4	32.1	10.4	21.0
low value	50.6	116.2	14.1	23.6	31.2	8.2	18.7
PMT resistance rate							
high value	47.3	99.3	15.4	26.6	32.7	9.6	21.1
low value	33.6	74.2	13.0	21.4	29.3	8.3	18.8

Table 2. Welfare Gain from Reducing ACT Price to $0.30: Further Sensitivity Analysis
(Discounted Welfare Gain, $ per capita)

	initial transmission rate			
	low	baseline	high	extreme
Baseline case	73.8	26.8	17.4	-0.9
Altruism parameter increased from 0 to				
0.1	77.8	44.6	35.9	1.2
0.3	85.9	80.1	72.9	5.3
0.5	94.0	115.6	109.9	9.4
Annual discount rate increased from 3% to 7%	49.6	17.7	10.6	-0.6
Producer price of ACT				
lowered to $0.90	69.4	30.3	20.8	-0.7
raised to $1.70	78.8	25.0	15.4	-1.0
Spontaneous recovery rates				
increased 25%	59.2	24.1	15.3	-1.1
decreased 50%	71.5	25.7	16.7	-0.6
Initial rate of immunity loss				
increased 50%	59.5	21.7	13.3	-0.5
decreased 50%	80.3	28.0	16.7	-1.0