Anti-Malarial Biotechnology, Drug Resistance, and the Dynamics of Disease Management

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Abstract

In the presence of market imperfections, there is no guarantee that society will benefit from technological change. This research analyzes the impact of biotechnology designed to bypass agricultural processes in the production of pharmaceutical products. High quality pharmaceuticals often exist alongside less effective treatments with a common active phytochemical ingredient. In this context, antimicrobial resistance generated by the consumption of one product also affects the efficacy of the other product. These interdependencies fundamentally alter the effects of biotechnology on retail markets, agricultural input markets, and antimicrobial resistance. I construct a dynamic epidemiological-economic model of the global market for anti-malarials to analyze the potential economic and public health costs associated with the introduction of a recently developed semi-synthetic production technology by which to procure artemisinin for use in artemisinin-based combination therapies (ACTs) used in the treatment of malaria. I find that in addition to decreasing the price of ACTs, semi-synthetic production technology also lowers the price of low quality monotherapy treatments and increases resistance to all forms of artemisinin. Despite these adverse effects, the development of semi-synthetic artemisinin leads to a present-value gain of approximately $2 billion in social welfare over a seven-year time horizon.

Key words

Artemisinin, Biotechnology, Drug Resistance

Introduction

Access to artemisinin-based combination therapies (ACTs) has contributed to a 47 percent reduction in the malaria mortality rate and a 24 percent reduction in the malaria case fatality rate from 2000 to 2013 (WHO, 2014). The active ingredient in artemisinin has traditionally been derived from *artemisia annua*, a plant grown primarily in China and Vietnam. Researchers at the University of California, Berkeley and Amyris, Inc. recently developed a method by which to produce artemisinic acid semi-synthetically using a genetically engineered bacterium. However, efficacious treatment may soon become infeasible. In many countries ACTs are marketed alongside less effective treatments that share common active ingredients. In this context, antimicrobial resistance generated by the consumption of one product also affects the efficacy of the other product. Past drug consumption and a variety of other conditions have already led to antimicrobial resistance to artemisinin-based combination therapies (ACTs), artemisinin monotherapies, and all feasible partner drugs, such that treatment has been rendered ineffective for at least some portion of the human population. The public health implications are substantial. Widespread resistance to ACTs could increase annual malaria-related deaths by over 116,000 and contribute an additional $417 million to the economic losses associated with the disease (Lubell et al., 2014).

The introduction of semi-synthetic ACT production technology will affect the availability and usage of all anti-malarials and has the potential to dramatically affect economic and public health costs. Yet, even if semi-synthetic production technology lowers the price of ACT treatment, widespread use of artemisinin monotherapies could dampen (or even reverse) the potential benefits. Use of semi-synthetic technology removes a large share of demand for plant-derived artemisininin. This inward demand shift lowers the price of procuring the active ingredient for use in monotherapies. If reductions in the price of monotherapies correspond to increased monotherapy consumption, antimicrobial resistance may stunt the benefits of increased access to ACTs.

To formally investigate the potential economic and public health effects resulting from the introduction of semi-synthetic artemisinin I integrate a mathematical epidemiology model of malaria transmission and drug resistance adapted to account for the geographic spread of resistance into a dynamic, partial equilibrium international trade framework representing the market for anti-malarials. Malaria-endemic countries are divided into two regions: one in which artemisinin monotherapies

are allowed, and the other in which monotherapies are banned. I depict the global market for anti-malarials using a two-region trade framework that allows me to account for the simultaneous interaction of several related markets over time. I model malaria transmission and drug resistance using the mathematical epidemiology model set forth in Laxminarayan et al. (2010), adapted to account for the spread of resistance across space. Infected individuals are heterogeneous with the respect to ability and willingness to pay for treatment and economic distance to the public health facility. Based on the menu of drug prices, drug efficacy, and travel costs, these individuals choose whether to seek treatment at the public health facility, purchase an anti-malarial at the local drug store, or forgo medication.

Despite reductions in the price of artemisinin monotherapies and increased resistance to all forms of artemisinin, I find that the development of semi-synthetic artemisinin leads to a present-value gain of approximately $2 billion in social welfare over a seven-year time horizon. Losses in surplus for growers of *artemisia annua* are more than offset by gains to infected individuals, donors and taxpayers, and the public at large. Increased global access to ACTs reduces the external costs associated with mortality and morbidity by five percent. Lower prices also reduce donor and taxpayer outlays and increase the surplus of households faced with a malaria episode.

Background

Malaria is a vector-borne infectious disease caused by parasitic protozoans that have been transmitted to humans through bites of infected female Anopheles mosquitoes. The disease is endemic to six World Health Organization (WHO) regions and is a risk for almost half of the global population. Table 1 reports the global burden of the disease. In 2013, malaria resulted in 198 million infections and 584 thousand deaths worldwide (WHO, 2014). The impact of the disease is heavily concentrated in the sub-Saharan African region. Due in part to high infection rates among small children, the region had the most cases, the most deaths, the most cases per capita, and the second highest case fatality rate among the six WHO regions in 2013.

Substantial progress has been made in recent years to reduce the global health impacts of the disease. Increased inter-governmental and non-governmental intervention efforts, including the mass distribution of insecticide-treated mosquito nets have reduced the annual disease incidence by 29 million cases worldwide and by 9 million cases in the Africa region since 2000 (WHO, 2014). During

this period, annual mortality has decreased by 298 thousand deaths, including a reduction of 273 thousand in sub-Saharan Africa (WHO, 2014).

[Table 1 about here.]

One of the main drivers in the massive reduction in mortality has been increased access to ACTs, which combine artemisinin with some other anti-malarial agent. ACTs are the most effective and fastest acting among all current treatments worldwide. Since the WHO first recommended ACTs as first-line treatment policy in 2002, the market for these drugs has expanded dramatically. Between 2005 and 2013, ACT production increased from 11 million to 392 million courses of treatment (WHO, 2014). ACTs have been adopted as the national malaria treatment policy in 79 of the 89 malaria-endemic countries (WHO, 2014).[1] Eleven pharmaceutical companies are now approved to manufacture ACTs, and the two largest manufacturers—Novartis Pharmaceuticals and Sanofi—provide the medicines at cost. Government policies have also been implemented to increase access to ACTs. Many countries, especially in Africa, provide the treatments at low or no cost to patients in public health facilities who have been diagnosed with malaria.

Yet, access to ACT treatment is still not universal. Less than 20 percent of malarial children in sub-Saharan Africa received ACT treatment in 2013 (WHO, 2014). Public health systems are difficult for rural patients to access and often do not function properly. A large proportion of patients go untreated or seek treatment with private sector vendors where ACTs are more expensive. The retail sector accounts for 40 to 97 percent of anti-malarial sales (Arnold et al., 2012). Moreover, a few formulations of ACT dominate global usage. The two most common forms of ACT—artemether-lumefantrine and artesunate plus amodiaquine—represent a combined 99 percent of ACT production (WHO, 2014).

Alongside access issues, ACTs are already losing efficacy in some regions. Resistance to artemisinin has been detected in five South-east Asian countries—Cambodia, Laos, Myanmar, Thailand, and Vietnam. Recent epidemiological research suggests that the prevalence and geographic spread of resistance may be even greater than previously believed (Tun et al., 2015).[2] Mutations in the

[1] Chloroquine is the first-line treatment in 10 Central American and Caribbean countries where it remains efficacious.

[2] The geographic spread of resistance to anti-malarial medicines is nothing new. Resistance to chloroquine—a previous WHO first-line treatment—emerged in South-east Asia in the late 1950s. Resistance spread through Europe, the Pacific, and sub-Saharan Africa and emerged independently in Latin American in the 1960s and 1970s. Today chloroquine remains effective in only a few Latin American countries.

K13 propeller gene in plasmodium falciparum parasites that strongly correlate with resistance to artemisinin have been found from Vietnam to Myanmar (Takala-Harrison et al., 2015). The consumption of artemisinin as a monotherapy rather than a combination therapy is less effective and hastens the development of antimicrobial resistance to artemisinin in both the monotherapy and ACT form (WHO, 2014).

Advocacy by the international community aimed at preserving the efficacy of artemisinin has led to a large reduction in the consumption of monotherapies. The World Health Assembly adopted a resolution supporting a ban on artemisinin monotherapies in 2007 (WHO, 2014). Yet, the problem presists. Two dozen pharmaceutical companies still market monotherapies, and several countries in sub-Saharan Africa, South-east Asia, and the Western Pacific do not restrict their use (WHO, 2014). Even in countries with outright bans, monotherapy consumption may not be eliminated completely. For example, a recent study found that artemisinin monotherapies represented 33 percent of private sector anti-malarial sales in Myanmar in 2012, even though the products were purportedly banned (White, 2013). The purchase and sale of low quality anti-malarials in the informal private sector can be difficult for countries with poor institutional capacity to regulate (Björkman-Nyqvist et al., 2012). Moreover, a range of products much wider than generic medications, such as dried *artemisia annua* leaves or or herbal teas, may contribute to artemisinin resistance.

Other drugs that are combined with artemisinin to create ACTs are also marketed in monotherapy form. These "partner" drugs are often of low efficacy and promote antimicrobial resistance to ACTs, but generic formulations can be produced at extremely low cost. Unlike artemisinin monotherapies, however, health officials have not called for a widespread ban on these products.

[Figure 1 about here.]

Artemisinin has traditionally been produced using chemicals extracted from *artemisia annua*, a crop grown primarily in central China and Vietnam. After harvest, the dried leaves are collected and sent for chemical extraction. The per hectare yield of artemisinic acid is heavily dependent on rainfall, climate, and other environmental factors (Shretta and Yadav, 2012). Due to the rapid increase in demand for ACTs following the WHO's endorsement in 2002 and poor weather in the Chongqing province of China, the price of harvested artemisinic acid reached $664 per metric tonne in 2005 (Shretta and Yadav, 2012). Farmers responded by increasing production, and by 2007

the price had fallen to $187.57 per metric tonne (Shretta and Yadav, 2012). A non-governmental organization known as The A2S2 Assured Artemisinin Supply System publishes monthly rolling data on the quantity and average unit value of plant-derived artemisinin. Data for January 2011 to January 2016 are reported in figure 1. Following the initial adjustment phase from 2002 to 2012, the market *artemisia annua* has adapted. Since April 2013, the price of artemisinic acid has steadily decreased to $173.42 per metric tonne in January 2016 (A2S2, 2015).

The period of rising and falling prices from 2008 to 2012 left many international agencies scrambling to "stabilize the supply" of artemisinin (Shretta and Yadav, 2012). Researchers proposed various technologies by which to produce artemisinin synthetically, but most were commercially infeasible (Paddon and Keasling, 2014; Shretta and Yadav, 2012). In late 2012, researchers at the University of California, Berkeley and Amyris, Inc. developed a method by which to produce artemisinic acid "semi-synthetically" using a genetically engineered production technology (Paddon et al., 2013).[3] In 2013 the WHO Prequalification of Medicines Programme approved semi-synthetic technology for use in the manufacture of active pharmaceutical ingredients. Sanofi Pharmaceuticals began large-scale production of semi-synthetic ACT treatments in late 2013. Production expanded in 2014. By the end of the year, Sanofi produced 115 million semi-synthetic treatments, or approximately 50 percent of annual ACT production worldwide (Palmer, 2014).

Literature Review

Since the modern re-discovery of artemisinin in 1981 by Youyou Tu, volumes of microbiological and epidemiological research have analyzed the chemical properties of the drug and its effects on parasitic resistance, but these issues have entered the economics literature only recently.[4] This study is related to three distinct, but interconnected, strands on the economics of malaria. The first strand integrates mathematical epidemiology models into an economic framework to assess the desirability of policy interventions to combat malaria. Since the seminal work by Koella (1991), models of malaria transmission and drug resistance have become increasingly complex, but production and household decision making processes are often dramatically simplified. Laxminarayan et al. (2010)

[3] The term "semi-synthetic" refers to the fact that early steps in the synthesis of the drug are accomplished via biological processes. Only the final stages of synthesis involve organic chemistry. Artemisinin that is procured semi-synthetically is indistinguishable from plant-derived artemisinin (Paddon and Keasling, 2014).

[4] Youyou Tu was awarded the 2015 Nobel Peace Prize for the modern re-discovery of artemisinin.

is the most rigorous analysis in this line of research. The authors investigate the effects of a global subsidy to ACTs using a model that accounts for resistance to multiple drugs. Consumer demand is characterized using a constant elasticity of substitution demand function. The price of drugs is fixed and independent of the quantity produced and consumed.

Another strand of literature analyzes the effects of drug pricing policies on household treatment-seeking behavior (Björkman-Nyqvist et al., 2012; Cohen et al., 2015, 2013). Of particular interest in this line of research is the interaction between drug prices and the decision to attend public versus private sector treatment facilities. Cohen et al. (2015) use an expected utility framework to assess whether a household will seek diagnosis at the formal health clinic, purchase drugs at the local drug shop, or forgo medication. The authors then use evidence from a randomized control trial in Kenya to investigate the relationship between private sector subsidies for ACTs and drug consumption. Throughout the analysis, drug prices are exogenous to the quantity demanded. Epidemiological implications are discussed in passing.

Formal economic analyses of the anti-malarial drug supply are limited. Kangwana et al. (2009), Patouillard et al. (2013), and Shretta and Yadav (2012) discuss issues related to ACT production but do not develop explicit models. The sole supply side model of ACT production is Kazaz et al. (2014). The authors develop a stochastic framework to model the ACT supply chain to assess the affects of various policy interventions. However, the analysis overlooks the interactions with related markets for artemisinin monotherapies and partner drugs. Epidemiological issues are largely ignored.

A Simple Static Framework

Before embarking on the formal analysis, I illustrate the effects of introducing semi-synthetic artemisinin using a highly stylized, static model. For this exercise, I assume that partner drugs are not marketed in monotherapy form. Figure 2 illustrates the global artemisinin supply chain from farm to end user. Vertical length K in panel (c) represents the initial efficacy of artemisinin in treating malaria. Consumption of artemisinin monotherapies and ACTs generates negative externalities by reducing efficacy for later treatments, but the external costs vary by product. A marginal increase in the consumption of ACTs generates a smaller externality than an equivalent increase in the consumption of monotherapies because the ACT partner drug slows the rate at which parasites develop resistance. In panels (a) and (b), E_{XY} and and E_X represent the externalities associated

with ACT consumption (Q_{XY}) and monotherapy consumption (Q_X), where $\frac{dE_{XY}}{dQ_{XY}} < \frac{dE_X}{dQ_X}$. Final efficacy is equal to the initial efficacy minus the sum of the externalities generated by consumption, i.e., $K - (E_{XY} + E_X)$.

[Figure 2 about here.]

Panels (d) and (e) of Figure 2 depict the global pharmaceutical retail markets. To model the effects of introducing semi-synthetic artemisinin on production, I depict the marginal cost curves for ACTs and monotherapies, S_{XY} and S_X, under two alternative production scenarios. In scenario one, artemisinin for use in monotherapies and ACTs is derived from *artemisia annua*. In the second scenario, an endogenous portion of ACTs is procured semi-synthetically. Monotherapies and the remaining portion of ACTs are plant-derived. Global demand schedules for ACTs and monotherapies, D_{XY} and D_X, are independent of the production scenario.

Supply and demand conditions in the retail markets uniquely imply the derived demands R_{XY} and R_X for *artemisia annua* in panels (f) and (g). In scenario one, the market clears when the total quantity of *artemisia annua* demanded, $R^1_{XY} + R_X = D_A$, is equal to the quantity supplied, S_A. Panel (h) depicts this equilibrium at price w^1. The amount of *artemisia annua* produced is A^1. Monotherapy producers use A^1_X tons of *artemisia annua* to produce Q^1_X monotherapy treatments, which are sold at price P^1_X. The consumption of monotherapies reduces the stock of efficacy by E^1_X in panel (b). ACT producers use A^1_{XY} tons of *artemisia annua* to produce Q^1_{XY} courses of ACT, which are sold at price P^1_{XY}. ACT consumption reduces efficacy by E^1_{XY}. Final efficacy, depicted in panel (c), is $K - E^1_{XY} - E^1_X$. Because consumers consider drug efficacy only to the extent that it impacts their own well-being and do not heed the effects of their consumption on future treatment, the outcome is sub-optimal (Miranowski and Carlson, 1986).

I model the introduction of semi-synthetic technology in the second scenario as a constant marginal cost production activity, where S^2_{XY} corresponds to a 10 percent cost savings relative to P^1_{XY}. The technology simultaneously pivots the derived demand for *artemisia annua* for use in ACT production to R^2_{XY}. Thus, the total demand for *artemisia annua* becomes D^2_A. This effect also pivots the monotherapy supply curve from S^1_X to S^2_X in panel (e). Again, the market clears when the demand for *artemisia annua*, now D^2_A, is equal to the quantity supplied. The price of *artemisia annua* falls to w^2.

Monotherapy producers use A_X^2 tons of the input to produce Q_X^2 monotherapy treatments, which are sold at P_X^2. The increase in monotherapy consumption increases the resistance externality from E_X^1 to E_X^2. ACT producers use $A^2 - A_X^2$ tons of *artemisia annua* to produce plant-derived ACTs. The remainder are procured semi-synthetically. The price of ACTs falls from P_{XY}^1 to P_{XY}^2, and the number of treatments increases from Q_{XY}^1 to Q_{XY}^2. The additional ACT consumption slightly increases the corresponding externality from E_{XY}^1 to E_{XY}^2.

Because the technological change lowers the price of both treatments, the net effect is a reduction in final efficacy to $K - E_{XY}^2 - E_X^2 < K - E_{XY}^1 - E_X^1$. For the reasons discussed above, the allocation between initial and final efficacy is sub-optimal. However, a comparison of the welfare effects in scenario 2 with those in scenario 1 is ambiguous. On one hand, consumers in scenario 2 benefit from low drug prices. On the other hand, the drugs are less effective than in scenario 1. The relative magnitudes of these effects and the extent to which they translate into gains or losses in social welfare are dependent on several market parameters.

One significant economic parameter that is not captured in figure 2 is the cross-price elasticity of demand for ACTs and artemisinin monotherapies. When the price of one product falls, consumers will likely substitute away from the other product in favor of the cheaper treatment. Because the prices of both treatments fall in this scenario, the direction of this effect is uncertain. This ambiguity is increased by the existence of the partner drug. A reduction in the price of the artemisinin monotherapy will likely induce some consumers to substitute away from low efficacy partner drug treatments in favor of artemisinin monotherapies, which are relatively more effective. Thus, the negative externality generated by increased artemisinin monotherapy consumption is also offset by a reduction in the externality generated by partner drug consumption. Moreover, to the extent that increased drug use by one individual reduces the risk that infection will be transmitted to others, the negative externality associated with drug resistance may be offset by a positive externality (Laxminarayan et al., 2010). The section that follows addresses these considerations.

Methodology

To formally investigate the potential economic and public health effects resulting from the introduction of semi-synthetic artemisinin I integrate a mathematical epidemiology model of malaria

transmission and drug resistance adapted to account for the geographic spread of resistance into a dynamic, partial equilibrium two-region trade framework representing the market for anti-malarials. This specification allows me to model the simultaneous interaction of several related markets over time. I allow consumption, resistance patterns, and government treatment policies to differ across regions. A comparison of two contrasting market scenarios demonstrates the effects of introducing semi-synthetic ACTs. In the baseline scenario ACTs and artemisinin monotherapies are procured from *artemisia annua*, the agricultural product. In the second scenario a portion of ACTs are procured from semi-synthetic production technology; artemisinin monotherapies and the remainder of ACTs are derived from *artemisia annua*.

[Figure 3 about here.]

Figure 3 provides a schematic representation of the model and characterizes the solution procedure. Global production of anti-malarials occurs in two stages. In the first stage of production, farmers grow *artemisia annua* and drug manufacturers derive an active "partner" ingredient using organic chemistry. In the second scenario, drug manufacturers also derive semi-synthetic artemisinin. In the second stage of production, pharmaceutical companies transform the artemisinic acid and partner ingredient into monotherapies or combine them to produce ACTs using fixed proportion technologies.

Malaria endemic countries are divided into two regions, A and B, which are identical in every respect except that artemisinin monotherapies have been successfully banned in region B. At any given time, the population in each region is sub-divided into three groups: (1) individuals who are susceptible to malaria infection, (2) individuals who are currently infected, and (3) people who have temporarily acquired immunity by fighting off an infection. Based on the menu of drug prices, drug efficacy, and travel costs, infected individuals decide whether to seek treatment at the public health facility, purchase an anti-malarial at the local drug store, or forgo medication. The global demand for anti-malarials is an aggregation across the total number of infected individuals by choice of treatment.

Global market equilibrium occurs when the derived demand for *artemisia annua* is equal to the agricultural supply and the global supply of each anti-malarial equals its global demand. In each region, consumption of a given drug induces a spontaneous mutation in the local parasite

population, such that a small portion of parasites becomes resistant to the drug. A fraction of these parasites are then transported from one region to the other through entomological or human migration. The new genetic characteristics of the parasite population dictate disease transmission and drug efficacy in the next period.

Epidemiological Framework

I rely heavily on the mathematical epidemiology model set forth in Laxminarayan et al. (2010) to characterize malaria transmission and drug resistance in each region. At time t, the population in each region is comprised of individuals who are susceptible to malaria infection (S), individuals who are currently infected (I), and individuals who have acquired temporary immunity (M). Three treatments options are available to infected individuals: the ACT (denoted by subscript XY), the artemisinin monotherapy (subscript X), and the partner drug (subscript Y). Thus, the infected population is further divided into four sub-groups: (1) those who are infected with a natural strain of the parasite that is not resistant to any drug (I_w), (2) those who are infected with a strain that is resistant only to the artemisinin monotherapy (I_x), (3) those who are infected with a strain that is resistant to the partner drug only (I_y), and (4) those who are infected with a strain that is resistant to both artemisinin and the partner drug, and are thereby resistant to ACTs (I_{xy}).[5] Drug resistance can arise spontaneously through genetic mutation, can be transmitted from one person to another through the vector, and can be imported from the other region.

Transmission. Let f represent the frequency at which people are bitten by mosquitoes. When a mosquito bites an infected human, the infection is transmitted to the mosquito with probability b_1. The mosquito mortality rate is δ^{mos}. In a given region, the fraction of the human population that is infectious with strain $i = w, x, y, xy$ is $\kappa_i = I_i/N$. Let l_i be the fraction of the population in the other region that is infectious with the corresponding strain. Infections spread from one region to another at rate ς via human and entomological migration.

Then the probability π_i that a mosquito will become infected with strain i during its life is

$$\pi_i = \frac{fb_1\left(\kappa_i + \varsigma \sum_j \kappa_i^j\right)}{\delta^{mos} + fb_1\left(\kappa_i + \varsigma \sum_j \kappa_i^j\right)}$$

[5] In this section and elsewhere, lower case subscripts $\{x, y, xy\}$ are used to refer to characteristics of strains resistant to treatment whereas subscripts $\{X, Y, XY\}$ generally refer to characteristics of the treatments themselves.

The probability that a mosquito will become potentially infectious to humans during its life is $e^{-\tau\delta^{mos}}\pi_i f/\delta^{mos}$. The number of susceptible mosquitoes that emerge per human per unit of time is m. Denote b_2 as the probability that a bite from an infectious mosquito will infect a human. The rate at which susceptible individuals in the region become infected with strain i is

$$h_i = b_2 m e^{-\tau\delta^{mos}} \frac{\pi_i f}{\delta^{mos}}$$

Thus, the total infection rate is $h = h_w + h_x + h_y + h_{xy}$.

Treatment. A fraction of people (a_i) in every infection sub-group receives treatment option $i\epsilon\{X, Y, XY\}$. When an individual carries a parasite that is not resistant to the treatment administered, one of three things can happen. In the majority of cases, occuring at rate ρ^{TR}, the individual recovers and returns to the susceptible population. Those who do not recover remain in the infected population. In a small percentage of cases, occuring at rate r_i, the use of treatment option j leads to a spontaneous mutation that is resistant to the drug.

A portion of individuals who do not receive treatment, or carry a parasite that is resistant to the treatment administered, acquire immunity. Let ρ_i^{SP} represent the rate at which immunity is acquired for individuals infected with strain i.[6] After a period of time, individuals lose immunity and return to the susceptible population. This process occurs at rate γ. Mortality occurs as a result of malaria at rate δ^I and as a result of non-malaria-related factors at rate δ^N. However, malaria-related and other deaths are exactly balanced by new births, B, which enter the susceptible population.

Equations of Motion. The relationships below describe how the six population sub-groups in each region change with respect to time. The schematic in figure 4 represents these equations of motion visually.

[Figure 4 about here.]

The susceptible population moves according to the following equation

[6] The spontaneous rate of recovery is greater for resistant infections than for wild-type infections, and is greatest for infections resistant to both drugs, i.e., $\rho_{XY}^{SP} > \rho_X^{SP}, \rho_Y^{SP} > \rho_W^{SP}$, because resistant strains face a 'fitness cost'.

$$\begin{aligned}\dot{S} =& -(h+\delta^N)S + \rho^{TR} I_w \sum_i a_i(1-r_i) + \rho^{TR} I_x(a_Y + a_{XY})(1 - r_y a_Y) \\ &+ \rho^{TR} I_y(a_X + a_{XY})(1 - r_x a_X) + \gamma M + B\end{aligned} \tag{1}$$

where the first term on the right-hand side represents individuals who leave the susceptible population as a result of infection or death. The second, third, and fourth terms represent individuals returning to the susceptible population after successful treatment. The fifth term represents individuals returning to the susceptible population after losing immunity.

Infected populations move according to the following four equations.

$$\dot{I_w} = h_w S - \rho^{TR} I_w \sum_i a_i - I_w(\rho_w^{SP}(1 - \sum_i a_i) + \delta^I + \delta^N) \tag{2}$$

$$\dot{I_x} = h_x S - \rho^{TR} I_x(a_Y + a_{XY}) + \rho^{TR} I_w r_x a_X - I_x(\rho_x^{SP}(1 - a_X - a_{XY}) + \delta^I + \delta^N) \tag{3}$$

$$\dot{I_y} = h_y S - \rho^{TR} I_y(a_X + a_{XY}) + \rho^{TR} I_w r_y a_Y - I_y(\rho_y^{SP}(1 - a_X - a_{XY}) + \delta^I + \delta^N) \tag{4}$$

$$\begin{aligned}\dot{I_{xy}} =& h_{xy} S + \rho^{TR}(I_w r_{xy} a_{XY} + I_x r_y(a_Y + a_{XY}) + I_y r_x(a_X + a_{XY})) \\ &- I_{xy}(\rho_{xy}^{SP} + \delta^I + \delta^N)\end{aligned} \tag{5}$$

The first term on the right-hand side of each equation represents individuals in the susceptible population who have acquired an infection. The second term in equations (2), (3), and (4) corresponds to individuals leaving the infected population after receiving effective treatment. This term does not appear in equation (5) because no effective treatment exists for the I_{xy} sub-group. The next term in equations (3), (4), and (5) correspond to individuals moving from one infected sub-group to another as a result of spontaneous mutations in the parasite population. The final term in each equation corresponds to individuals who leave the infected populations by acquiring immunity or dying.

The immune population moves according to the following equation:

$$\begin{aligned}\dot{M} =& \rho_w^{SP} I_w(1 - \sum_i a_i) + \rho_x^{SP} I_x(1 - a_Y - a_{XY}) \\ &+ \rho_y^{SP} I_y(1 - a_X - a_{XY}) + \rho_{xy}^{SP} I_{xy} - (\gamma + \delta^N)M\end{aligned} \tag{6}$$

The first four terms on the right-hand side of equation (6) describe individuals who enter the immune population by fighting off the infection. The final term describes individuals who leave the

population after losing immunity or dying of non-malaria-related causes.

Economic Framework

The fraction of infectious individuals treated with drug i (a_i) is a central determinant for the epidemiological relationships described in equations (1) through (6). This variable is non-random and inherently endogenous. Individuals and households faced with an infection decide whether to seek treatment and what form of treatment to seek based on the cost (and benefits) of all available options. A realistic representation of this decision process is critical to understanding the impacts of semi-synthetic ACT production on public health outcomes. Moreover, if the global drug supply is upward sloping, the price of treatment depends on the quantity demanded. In this section I develop an economic framework to characterize the household decision and derive equations for the global supply and demand for anti-malarials. Outcomes are integrated with the epidemiological framework through variables a_i, the fraction of the infected population that receives treatment i, and I_i, the fraction of the infected population that carries a strain that is resistant to drug i. I measure the economic and public health benefits associated with the introduction of semi-synthetic artemisinin using the concept of social welfare.

Demand. Households faced with an episode of malaria have a finite set of possible actions. They can choose to seek treatment at the public health facility, purchase an anti-malarial at the local drug store, or forgo medication. To represent the simultaneous trade-offs between public and private health facilities and drugs of differing qualities, I use a two-step consumer demand framework based on well-known horizontal and vertical differentiation models (Hotelling, 1990; Mussa and Rosen, 1978). I represent each region by a line whose length is normalized to unity. A public health facility lies at the rightward end of the line in the urban area. Households and drug stores are distributed uniformly along the line. Those located nearest to the public health facility represent populations in urban areas. As one moves leftward along the line, the population becomes increasingly remote.[7] Households first decide whether to attend the public health facility or purchase drugs at the local drug shop. Those that seek treatment at the public health facility receive ACTs for free but incur a per unit travel cost, λ, which is the sum of transportation costs and the value of lost time.

[7] The concepts of "urban" and "rural" are used for illustrative purposes. More precisely, the location of a household along the line represents the economic distance to public health facilities. In reality, this distance may have little to do with spatial distance or population density.

Households in region A that visit the local drug shop purchase a course of either the ACT, the artemisinin monotherapy, or the partner drug or forgo medication. They must pay full price for medication but do not incur the travel cost. A household located at address, d, on the line receives indirect utility

$$V(K, C; \theta) = \theta K_i - C_i$$

from consuming one course of treatment $i\epsilon\{XY, X, Y, Self\}$, where K represents the effectiveness of the chosen treatment, defined as the share of the infected human population that carries a strain of malaria that is susceptible to treatment i. For example, the efficacy of the artemisinin monotherapy is the share of the infected population that carries the wild strain or the partner-drug resistant strain, i.e., $K_X = \frac{I_w + I_y}{I}$. The total cost of obtaining treatment is C, where

$$C = \begin{cases} Pi & \text{if the household purchases treatment } i \text{ at the local drug shop} \\ \lambda(1-d) & \text{if the household seeks treatment at the public health clinic} \end{cases}$$

Willingness and ability to pay for effective treatment varies across households. Parameter θ, which takes values between 0 and 1, is a household-specific index that represents this heterogeneity. The distributions of household address and preference for drug efficacy are independent.

I solve for market level demand in region A using a two-step process. I first determine which anti-malarial drug each household would purchase given only the option to seek treatment at the local drug shop. This is accomplished by solving for the value of the θ parameter for the household that is indifferent between purchasing the ACT and the artemisinin monotherapy. All households with θ parameter higher than the indifferent household purchase ACTs. Using a similar procedure I determine which households would prefer to seek treatment at the public clinic rather than the local drug shop.

The box of height and length one in panel (a) of figure 5 represents the entire infected population, I, of region A in (d, θ) space. At any point in the box, a vertical move corresponds to households of higher willingness and ability to pay for treatment. A rightward move corresponds to households located nearer to the public health clinic. This representation is useful for visualizing demand equations (7) through (10).

[Figure 5 about here.]

Given only the option to purchase at the local drug shop, $\theta_i, i\epsilon\{XY, X, Y\}$ is the preference parameter of households indifferent between receiving treatment i and the closest treatment of lower efficacy. Households with preference parameter above θ_i, but below the indifference parameter for the next treatment of higher efficacy, would purchase treatment i. Thus, if the public clinic did not exist, the demand for ACTs would be $a + b$, the demand for artemisinin monotherapies would be $c + e$, and the demand for the partner drug would be $f + g$. Households in area $h + i$ would not receive treatment.

Segment d_{XY} describes the location of all households who are indifferent between purchasing the ACT at the local drug shop or traveling to the clinic. Because there is no trade off between the efficacy of treatment received at the clinic versus the local drug shop for those purchasing an ACT, d_{XY} is perfectly vertical. Segments d_Y, d_X, and d_{Self} describe the location of households who are indifferent between the same trade off for artemisinin monotherapies, the partner drug, and foregoing treatment, respectively. The slope of these segments is finite and decreasing as one moves from d_X to d_Y and from d_Y to d_{Self} because households in this portion of the box would receive a more effective treatment at the clinic than they would have at the drug shop. However, as one moves downward along θ, the subjective valuation of this trade-off also diminishes. The household with preference parameter $\theta = 0$ is indifferent between traveling a distance of ϵ to receive a free ACT at the clinic or foregoing treatment because the willingness and ability to pay for treatment is zero. Thus, segment d_{Self} intersects with the location of the clinic at the intercept.

Define l as the concatenation of segments $\{d_{XY}; d_X; d_Y; d_{Self}\}$. Households to the right of l in areas b, e, g, and i attend the clinic. Households on the left purchase at the local drug shop. Thus, as described in equation (7), the total demand for ACTs is $a + b + e + g + i$. Areas c and f, respectively, are the demands for artemisinin and partner drug monotherapies from equations (8) and (9). Households in area h do not receive treatment correspond to equation (10).

Panel (a) of figure 5 depicts the "everywhere-interior" solution in which all drugs are purchased at the local drug shop and a portion of households for each θ parameter choose not to travel to the clinic. Panel (b) depicts the two types of corner solutions that exist. The first type of corner solution involves cases where one or more of the drugs is not purchased at the local drug shop. The

demand functions for locally purchased drugs and clinical visits change in this situation. Consider, for example, the case where $\theta_X = \frac{P_X - P_Y}{K_X - K_Y} > \frac{P_{XY} - P_X}{K_{XY} - K_X} = \theta_{XY}$. In these circumstances, the artemisinin monotherapy is not purchased at the local drug shop. The integral in equation (9) describing the demand for the partner drug now runs from θ_Y to θ_{XY}. l becomes discontinuous between segments d_{XY} and d_Y. In the second type of corner solution, there exists some $\tilde{\theta}$, such that all households with $\theta > \tilde{\theta}$ choose to travel to the clinic. In this case l is kinked at $(0, \tilde{\theta})$ and vertical on the interval $[\tilde{\theta}, 1]$.

Vertical preferences are expressed analytically as follows.

- Households with taste parameter θ, such that $\theta_{XY} = \frac{P_{XY} - P_X}{K_{XY} - K_X} \leq \theta \leq 1$ prefer to purchase the ACT.
- Households with taste parameter θ, such that $\theta_X = \frac{P_X - P_Y}{K_X - K_Y} \leq \theta \leq \theta_{XY}$ prefer to purchase the artemisinin monotherapy.
- Households with taste parameter θ, such that $\theta_Y = \frac{P_Y}{K_Y} \leq \theta \leq \theta_X$ prefer to purchase the partner drug.
- Households with taste parameter θ, such that $0 \leq \theta \leq \theta_Y$ prefer to forgo treatment.

Incorporating these vertical preferences into the travel decision, I derive the complete set of preferences as follows.

- Households located at all points d, such that $d_{XY} \leq 1 - \frac{P_{XY}}{\lambda} \leq d \leq 1$ with taste parameter $\theta \epsilon [\theta_{XY}, 1]$ attend the clinic.
- Households located at all points d, such that $d_X = 1 - \frac{\theta(K_{XY} - K_X) + P_X}{\lambda} \leq d \leq 1$ with taste parameter $\theta \epsilon [\theta_X, \theta_{XY}]$ attend the clinic.
- Households located at all points d, such that $d_Y = 1 - \frac{\theta(K_{XY} - K_Y) + P_Y}{\lambda} \leq d \leq 1$ with taste parameter $\theta \epsilon [\theta_Y, \theta_X]$ attend the clinic.
- Households located at all points d, such that $d_{Self} = 1 - \frac{K_{XY}}{\lambda}\theta \leq d \leq 1$ with taste parameter $\theta \epsilon [0, \theta_Y]$ attend the clinic.

These relationships produce the following market demand functions for region A.

$$q_{XY} = (1 - \theta_{XY}) + \int_{\theta_X}^{\theta_{XY}} (1 - d_X)\, d\theta + \int_{\theta_Y}^{\theta_X} (1 - d_Y)\, d\theta + \int^{\theta_Y} (1 - d_{self})\, d\theta \tag{7}$$

$$q_X = \int_{\theta_X}^{\theta_{XY}} d_X\, d\theta \tag{8}$$

$$q_Y = \int_{\theta_Y}^{\theta_X} d_Y\, d\theta \tag{9}$$

$$q_{Self} = \int^{\theta_Y} d_{Self}\, d\theta \tag{10}$$

In region B, where monotherapies are banned, the household decision and aggregation procedure are identical except that consumers do not have the option to purchase artemisinin monotherapies at the drug shop. Global demand for each product, D_i, is the sum of demand in each region weighted by the regional share of global malaria incidents.

Supply. Global production of anti-malarials occurs in two stages. First, farmers grow *artemisia annua*, and pharmaceutical companies manufacture the partner drug. The marginal cost of producing *artemisia annua*, w_A, increases with the quantity demanded, i.e., $w_A = \mathrm{f}(Q_{XY} + Q_X)$. This assumption reflects the fact that production is geographically constrained. Artemisinic acid must be of sufficient potency to treat malaria, and potency is highly dependent on specific agrological-climatic conditions. I assume that the manufacture of the partner drug is a synthetic process, and even in the short run firms have excess capacity and can increase or decrease production at a constant marginal cost, w_Y. Pharmaceutical companies transform *artemisia annua* and the partner drug into monotherapies or combine them to produce ACTs using fixed proportion technologies. Thus, I can specify the marginal cost of producing each product as $MC_i = w_i + c_i$, where c_i is a constant, product-specific transformation cost, which includes the costs of all additional inputs.

In the first scenario all artemisinin monotherapies and ACTs are procured from *artemisia annua*. The price of inputs is

$$w_i = \begin{cases} w_A & \text{for artemisinin monotherapies} \\ w_Y & \text{for the partner drug} \\ w_A + w_Y & \text{for the ACT} \end{cases}$$

For simplicity I assume farm-level supply is unit elastic, which, after normalization, implies the price of the input is $w_A = Q_{XY} + Q_X$. In the second scenario, a portion, ψ, of ACTs are produced using the semi-synthetic technology at constant marginal cost w_S.[8] The remainder of ACTs are derived from *artemisia annua*. The price of *artemisia annua* becomes $w_A = Q_X + (1-\psi)Q_{XY}$. Drugs sold at local shops are priced at marginal cost.

Market Equilibrium. I solve for global market equilibrium by equating derived demand for *artemisia annua* with agricultural supply and equating the global supply of anti-malarials with the global demand. Because populations have been normalized to unity, the quantity demanded, q_i, in each region corresponds directly to a_i from the epidemiological framework. In the second scenario, ACT producers are indifferent between deriving artemisinin from *artemisia annua* or procuring it semi-synthetically. Thus, the market clearing price for plant-derived artemisinin is equal to the marginal cost of producing semi-synthetic artemisinin.

Social Welfare. Common variables used to measure the welfare impacts of disease interventions include direct costs to taxpayers and donors associated with the provision of drugs, clinics, and physicians and external costs, such as losses in productivity and economic growth, resulting from sickness and death (Gallup and Sachs, 2001; Laxminarayan et al., 2010; Lubell et al., 2014). In addition to these variables, I include the concepts of consumer and producer surplus in the welfare calculation. In addition to increasing access to treatment, a change in the price of anti-malarials has a direct impact on household well-being. Money (or time) formerly used to purchase an anti-malarial can now be used in other ways. I use consumer surplus as an aggregate measure of this impact. Finally, the effects of semi-synthetic artemisinin are more widespread than the those seen in pharmaceutical markets and in the transmission of malaria and drug resistance. The technology will reduce demand for plant-derived artemisinin, and thus, negatively affect farmers of *artemisia annua*. Producer surplus is included to capture these broader economic impacts.

Social welfare is quantified as the present value sum of the consumer surplus, producer surplus,

[8] The data reported in figure 1 lend credence to the assumptions that semi-synthetic technology lowers the cost of production. Prior to the widespread rollout of semisynthetic artemisinin in January 2014, the average unit price of artemisinin imported into India was $475.59 per kilogram. Since January 2014, the average unit price has dropped to $224.65. The data also lend credence to the assumption that semi-synthetic production is a constant marginal cost activity. Prior to the introduction of semi-synthetics, the correlation between the quantity of imports and their average unit value is -0.22. The standard deviation of the price series is 127.00. Once semi-synthetics are introduced, the correlation between imports and unit value and the standard deviation of the unit value series fall to 0.03 and 29.91, respectively.

external costs, and donor and taxpayer outlays associated with mortality and morbidity accumulated over the period of analysis. These calculations are straightforward. Consumer surplus for households that purchase ACTs at the local drug shop in a given period is

$$\int^{d_{XY}} \int_{\theta_{XY}}^{1} (\theta K_{XY} - P_{XY}) \, \mathrm{d}\theta \, \mathrm{d}d$$

Consumer surplus for households that purchase the artemisinin monotherapy is

$$\int^{d_X} \int_{\theta_X}^{\theta_{XY}} (\theta K_X - P_X) \, \mathrm{d}\theta \, \mathrm{d}d$$

Consumer surplus for households that purchase the partner drug is

$$\int^{d_Y} \int_{\theta_Y}^{\theta_X} (\theta K_Y - P_Y) \, \mathrm{d}\theta \, \mathrm{d}d$$

And the consumer surplus for households that receive ACT treatment at the public health clinic is

$$\int_0^{\theta_Y} \int^{d_{self}} (\theta K_{XY} - \lambda d) \, \mathrm{d}d \, \mathrm{d}\theta + \int_{\theta_Y}^{\theta_X} \int^{d_Y} (\theta K_{XY} - \lambda d) \, \mathrm{d}d \, \mathrm{d}\theta +$$
$$\int_{\theta_X}^{\theta_{XY}} \int^{d_X} (\theta K_{XY} - \lambda d) \, \mathrm{d}d \, \mathrm{d}\theta + \int_{\theta_{XY}}^{1} \int^{d_{XY}} (\theta K_{XY} - \lambda d) \, \mathrm{d}d \, \mathrm{d}\theta$$

Donors and taxpayers purchase the ACTs provided to patients at public health clinics at marginal cost. Thus, the total outlay from donors and taxpayers is $P_{XY} \int_0^1 (1 - l) \, \mathrm{d}\theta$. Producer surplus is $\int_0^{w_A} (Q_X + Q_{XY}) \, \mathrm{d}w$ in the first scenario, and $\int_0^{w_A} (Q_X + \psi Q_{XY}) \, \mathrm{d}w$ in the second scenario. The external cost associated with mortality and morbidity is $(c^I I + c^\delta \delta^I I)$ where c^I and c^δ are constant-per-unit monetary values.

Calibration and Sensitivity Analysis

I simulate the model set forth above on a quarterly time-step over a period of 7 years. I choose this relatively short time horizon because advances with other health innovations, such as the introduction of genetically modified mosquitoes or the development of a high efficacy vaccine, may fundamentally alter epidemiological and economic relationships in the medium- to long-run. This

section discusses the calibration of parameters and considers the sensitivity of results to the chosen specification.

Epidemiological Variables. With the exception of ς, which represents the spread of resistance across space, all epidemiological variables are calibrated using the baseline values from Laxminarayan et al. (2010). I report calibrated values in table 2 rather than repeat the justifications of those authors here.[9] Laxminarayan et al. (2010) use no-drug, steady-state population shares to classify initial population sub-groups. In contrast, I use estimates from WHO (2014) to classify the initial susceptible, infected, and immune populations and to allocate individuals among sub-groups in the infected population. Fifteen percent of the population in both regions is infected in the first period. Five percent are immune, and the remainder are susceptible. Country-level therapeutic efficacy studies for anti-malarial medicines suggest that approximately 0.01 percent of current parasite strains are resistant to ACTs.[10] The share of parasites resistant to artemisinin monotherapies and partner drugs are found in approximately 0.10 and 0.50, respectively.

[Table 2 about here.]

To isolate the implications of these calibrated values, I investigate two contrasting treatment specifications using a reduced, single-region version of the epidemiological framework in which economic behavior is removed. In the first specification, all treatment is eliminated, i.e., $a_i = 0, i \epsilon X, Y, XY$. In the second, the *status quo*, or initial equilibrium level of drug consumption for region A, persists over the entire time horizon.[11] Panels (a) and (b) of figure 6 depict the hypothetical impacts on disease dynamics and drug efficacy. Solid lines in both panels correspond to the "no treatment" outcomes, and dashed lines correspond to the *status quo*.

[Figure 6 about here.]

As seen in panel (a), if treatment is eliminated, the infected share of the population increases substantially over time. By the seventh year, the infected population has grown by over 85 percent. Perhaps surprisingly, the situation is almost as bleak under *status quo* levels of treatment. By the

[9] Note that some values in table 2 have been modified to account for the fact that I use a quarterly, rather than daily, time step.

[10] The data for these efficacy studies are accessible at the WHO global antimalarial drug efficacy database: `http://www.who.int/malaria/areas/drug_resistance/drug_efficacy_database/en/`.

[11] This *status quo* corresponds to 44 percent of the infected population treated with ACTs, 18 percent treated with the artemisinin monotherapy, and 13 percent treated with the partner drug.

seventh year, the infected share has increased by over 40 percent. Panel (b) sheds light on this outcome. High levels of artemisinin monotherapy and partner drug consumption in the *status quo* case lead to a large reduction in efficacy across all drug categories. The time paths for the *status quo* specification in panels (a) and (b) lends support for this finding. Drug efficacy remains fairly high through the second quarter of year two. At this point, the infection level is 75 percent less than in the "no treatment" case. However, as efficacy falls and a greater share of treatments begin to fail, the level of infections rises. Thus, by the end of year 7, the *status quo* level of infection is only 25 percent lower than in the no treatment case.

Turning to the "no treatment" case in panel (b), the efficacy of all drug categories increases rapidly due to the evolutionary advantage of the natural, or "wild", strain. By the seventh year, the efficacy of artemisinin monotherapies has increased to 0.96 and the efficacy of partner drugs has increased to 0.84. ACTs are approximately 0.9999 percent effective by this time. The actual time path for drug efficacy will likely lie somewhere between the two extremes shown in panel (b) because, as the efficacy of a drug diminishes, households will substitute away from the product; thereby preserving its efficacy. Under these circumstances, infection levels will almost certainly lie everywhere below those depicted in panel (a).

To the author's knowledge, this is the first research to incorporate a multi-region specification into an integrated economic-epidemiological framework. As such, no prior estimates of ς, the geographic spread of resistance, exist. Yet, the concept is paramount to understanding the effects of semi-synthetic artemisinin production technology. If resistance in South-East Asia were to spread into the Indian sub-continent or sub-Saharan Africa, the global health implications could be substantial. The downward pressure on artemisinin monotherapy prices resulting from the introduction of semi-synthetic production technology increases the likelihood of these outcomes.

Many of the spatial aspects of resistance remain mysterious to epidemiologists. The rate at which resistance spreads is not well understood.[12] To identify a reasonable value for this parameter, I combine the two cases depicted in panels (a) and (b) of figure 6 with a two-region framework. In region A treatment is distributed according to the initial *status quo*. In region B, no treatment is available.[13] When $\varsigma = 0$, regions A and B are completely isolated from each other, and there is

[12] Even the primary mechanism by which resistance spreads across space is not well known. For a discussion of these issues see, e.g., the introduction of Takala-Harrison et al. (2015).

[13] Again, economic behavior is not included in this specification.

no spread of resistance. Thus, drug efficacy in region B corresponds to the "no treatment" case in panel (b). When $\varsigma = 1$, any resistance established in region A flows freely to region B, and vice versa. The two regions function as a single entity.

Panel (c) of figure 6 shows the impacts of the spread of resistance on drug efficacy in region B under a range of values between 0 and 0.02. For value $\varsigma = 0.015$, the spread of resistance exactly offsets fitness costs, such that by the end of the seventh year the efficacy of ACTs remains unchanged. Because of the uncertainty associated with this parameter, I opt for the more conservative calibration of $\varsigma = 0.01$ under which the regions are relatively isolated. Fitness costs slightly outweigh spatial resistance patterns. With these assumptions in mind, I turn to the calibration of economic parameters.

Economic Variables. The Clinton Health Access Initiative provides information regarding the conversion rate for artemisinin into ACTs and artemisinin monotherapies (CHAI, 2009). I convert the average unit price of artemisinin imports into India for January 2016 from figure 1 to suggest that the current cost of procuring plant-derived artemisinin is approximately \$0.25 per treatment. The India import price is desirable because a majority of pharmaceutical firms that manufacture artemisinin monotherapies are located in the country. Health Action International (2012) reports prices for anti-malarial drugs at various sites across six countries. Because I have assumed the agricultural supply curve is unit elastic, I need only specify its slope. I choose the slope 0.22 so that the initial-equilibrium price of *artemisia annua* is equal to observed costs of procuring plant-derived artemisinin.

I assume drugs are priced at marginal costs, I calibrate the transformation costs for ACTs and artemisinin monotherapies, c_X and c_{XY}, as the difference between average drug prices and the annual average price of artemisinin imported into India in 2012. Calibrated values are $c_{XY} =$ \$0.625 and $c_X =$ \$0.375. The marginal cost of producing the partner drug is $w_Y =$ \$0.375 per treatment. The Global Fund also provides estimates on unit costs for various ACTs (Fund, 2010). My calibrations fall well-within the range of these estimates. The cost of producing semi-synthetic artemisinin is 10 percent less than the initial equilibrium price of artemisinin under the traditional production scenario, i.e., $w_S =$ \$0.7875. This assumption is also in line with early estimates by the Global Fund.

[Figure 7 about here.]

Various authors have attempted to quantify the opportunity cost of travel in seeking treatment for malaria. Asenso-Okyere and Dzator (1997) find that travel costs are not insubstantial and are roughly equivalent in magnitude to the price of treatment itself. Figure 7 plots the relationship between travel costs and global treatment seeking behavior in my model. I calibrate the cost of travel as $\lambda = 0.85$. This calibration produces estimates of current anti-malarial consumption, both in terms of product choice and the locus of treatment, that are consistent with a large body of literature (Arnold et al., 2012; Cohen et al., 2015; Davis et al., 2013; International, 2012; WHO, 2014). In the first period equilibrium, 36 percent of households seek treatment at the local drug shop, and 36 percent of households seek treatment at the public clinic. The remainder of infected individuals go untreated.

As described in the previous section, the population in region A has been normalized to unity. I assume region B, in which artemisinin monotherapies are banned, is 80 percent more populous than region A. Though the functionality of bans on monotherapy usage remains to be seen, the products are probably unavailable for a large share of the population in malaria-endemic regions.

[Figure 8 about here.]

The calibration of regional populations, travel costs, and the distributional assumptions about θ and d imply the global demand curves in figure 8. Each panel shows the share of the global infected population receiving drug i as a function price and efficacy. Efficacy and prices of all other drugs are held constant at initial (period one) levels. Panel (a) shows the global demand for ACTs. At low prices and high levels of efficacy, the ACT is purchased at local drug shops in both regions. In this zone of the diagram, ACTs completely crowd out other drugs at the local shop. Thus, demand is extremely sensitive to changes in price and effectiveness. At higher prices and lower levels of efficacy, global demand for ACTs becomes less sensitive as a greater proportion of consumers purchase other drugs at the local shops. Eventually, the ACT is no longer purchased at the drug shop in region A.

For two reasons, ACT demand is positive and responsive to changes in price and drug efficacy over the entire range plotted in panel (a). First, a large portion of consumers continue to travel to the clinic where they receive the ACT for free. However, as efficacy decreases, the benefits of

traveling to the clinic decrease, and some consumers choose to purchase a lower efficacy drug at the local shop. Second, only the ACT and the partner drug are marketed at the local shop in region B. Because the products are more differentiated in terms of price and efficacy, competition between drugs is less intense. ACTs are purchased even at high prices and low levels of efficacy.

The demand schedule in panel (b) for artemisinin monotherapies differs markedly from panel (a). At high prices and low levels of efficacy, monotherapies are completely crowded out of the market. Monotherapies enter the market according to a linear relationship between price and efficacy. Demand then slopes steeply in both price and efficacy directions as the monotherapy simultaneously displaces demand for ACTs and partner drugs. The rapid increase in monotherapy demand continues until other drugs have been completely crowded out of the retail sector. Again, this occurs according to a linear relationship between price and efficacy. Because an increase in the efficacy or decrease in the price of artemisinin monotherapies may lead a consumer to purchase a monotherapy rather than travel to the clinic, monotherapy demand continues to increase beyond this threshold. However, this displacement occurs at a much slower rate.

The relationship between price, efficacy, and demand for the partner drug in panel (c) is qualitatively similar to that for the artemisinin monotherapy, except that the initial price and efficacy of the drug is substantially lower. In the section that follows, I simulate the calibrated model to determine the impact of introducing semi-synthetic artemisinin. I calculate the present value of welfare streams using a standard 3 percent annual discount rate. As in Laxminarayan et al. (2010), morbidity and mortality costs are 6.3 cents and 20.5 cents, respectively, per day of infection.

Results

I find that the development of semi-synthetic artemisinin leads to a present-value gain of approximately $2 billion in global welfare. External costs associated with mortality and morbidity fall by five percent because a higher portion of the population has access to ACTs. Lower treatment prices also generate a 5.33 percent increase in surplus for households faced with a malaria episode. Though semi-synthetic artemisinin reduces surplus for farmers of *artemisia annua*, the technology eases the burden on donors and taxpayers by reducing the cost of providing care at public health facilities and inducing households to seek treatment at local drug shops. Outlays fall by 36 percent.

Table 3 reports treatment outcomes under each scenario. For brevity, only the first quarter of each year is included. Table 4 quantifies results in social welfare terms. Results are disaggregated by region and source of treatment (clinic versus retail).

[Table 3 about here.]

Scenario One: All artemisinin is plant-derived.

As shown in table 3, 40 percent of the infected population in region A seek treatment at the public clinic under scenario one. A further 35 percent of the population seeks treatment at the local drug shop. Only a small fraction of these individuals purchase the ACT. The share of the total infected population in region A that receives an ACT is 44 percent. Eighteen percent of individuals are treated with the artemisinin monotherapy, and thirteen percent receive the partner drug. The total fraction of the infected population that receives treatment is 0.75. The remainder go untreated. The first diagram in figure 9 depicts these results visually in (d, θ) space. Initial values occur in the "everywhere-interior" region of the diagram.

[Figure 9 about here.]

Figure 10 depicts the dynamic effects of equilibrium consumption on the efficacy of the three drugs. Household treatment-seeking behavior in the first scenario does preserve drug efficacy relative to the *status quo* results in panel (b) of figure 6, but the efficacy of all drugs diminishes over time. By year seven, 83 percent of infected individuals in region A carry a strain of parasites susceptible to ACT. The efficacy of artemisinin as a monotherapy decreases more slowly. By the final year, 80 percent of parasite strains are susceptible to the artemisinin monotherapy. The efficacy of the partner drug decreases to 41 percent.

[Figure 10 about here.]

Returning to table 3, one sees that changes in drug efficacy have a substantial impact on treatment choices in region A. By the seventh year, the relative efficacy of ACTs has decreased in relation to the alternative treatment options. Accordingly, only 38 percent of households choose to travel to the clinic in the seventh year. No ACTs are purchased at the local drug shop. Artemisinin monotherapy consumption decreases by one percent to 17 percent of the infected population. In

contrast, consumption of the partner drug increases to 19 percent of infected individuals. A diagram of the seventh year outcome is depicted in the bottom left-hand diagram of figure 9. Over time, the price of ACTs relative to the price of the artemisinin monotherapy decreased slower than the relative product efficacy. Equilibrium outcomes in the seventh year correspond to the corner solution where $(P_{XY} - P_X)/(K_{XY} - K_X) > 1$.

[Table 4 about here.]

Table 4 reports welfare outcomes in present value terms. The total surplus of infected individuals in region A who attend the clinic over the time horizon is $1.5 billion under scenario one. The total surplus of individuals who purchase anti-malarials from the local drug shop is $0.3 billion. Three factors explain the substantial difference in the surplus accruing to individuals who attend the clinic relative to those who purchase at the local drug shop. First, a majority of individuals attend the public health clinic. Accordingly, the clinic is where the majority of surplus accrues. Second, individuals who attend the clinic receive the ACT for free (net of travel costs). Because individuals in or near urban areas face small travel costs, this subsidy results in substantial surplus. In contrast, individuals who purchase at the local drug shop must pay market prices regardless of their location. Finally, consumption of the ACT is associated with higher levels of surplus because it is more effective than alternative forms of treatment. External costs associated with mortality and morbidity are approximately $10.8 billion in region A. The malaria-related loss in surplus in the region is approximately $9 billion.

Though the concept of donor and taxpayer outlays is included in the global welfare calculations, I exclude it from the regional welfare calculations. International bodies like the Global Fund that subsidize anti-malarials usually do so on a per-treatment basis rather than a per-country pre-allocation. The benefits of these subsidies accrue in the form of consumer surplus for individuals who attend public health clinics. However, because the funds are not tied to individual regions, the costs accrue to third parties.[14]

Scenario one results for region B are reported in table 3 starting in column one, row twelve. These outcomes differ slightly from those in region A. The ban on artemisinin monotherapies affects

[14] As of 2015, a small portion of funds is allocated on a per-country basis under the Affordable Medicines Facility. Because I have not distinguished between subsidy sources in the model, I do not dis-aggregate this type of country-based subsidies from other sources.

the consumption of all anti-malarials. Most consumers that would have purchased the artemisinin monotherapy in the absence of the ban choose instead to purchase the ACT in the first period. Approximately 18 percent of the population purchases the ACT at the local drug shop. The public clinic treats a further 42 percent of the infected population. Thus, the total share of the population receiving the ACT is 0.59. Sixteen percent of individuals use the partner drug. As in region A, one quarter of the population goes without treatment because the price of the partner drug is constant. The first period outcome in region B is depicted in (d, θ) space in the top right diagram in figure 9.

Turning to figure 10, the dynamics of drug efficacy also differ from those in region A. The ban on monotherapies in region B slightly preserves the efficacy of ACTs relative to region A. In the final year, 85 percent of infected individuals carry a parasite strain that is susceptible to the ACT. The ban also maintains the susceptibility of parasites to artemisinin as a monotherapy. In the seventh year, artemisinin monotherapies are over 83 percent effective. In contrast, the ban on artemisinin monotherapies increases the consumption of the partner drug relative to region A. Efficacy of the partner drug decreases to 39 percent. Treatment choices in region B are somewhat surprising in light of these dynamics.

The share of individuals seeking treatment at the clinic, reported in row twelve of table 3, falls from 0.42 in the first period to 0.33 in the seventh year. Consumption of the ACT at the local drug shop decreases, but not as quickly. The consumption share falls by 0.04 to 0.14 in the seventh year. In contrast, the share of individuals that purchase the partner drug increases from 0.16 in the first period to 0.26 in the seventh year. Figure 9 sheds light on these outcomes. Threshold values $\theta_{XY} = \dfrac{P_{XY} - P_X}{K_{XY} - K_X}$ and $\theta_Y = \dfrac{P_Y}{K_Y}$ in region B both increase over the time horizon, but θ_{XY} increases faster than θ_Y. Said in words, a fraction of consumers choose not to seek treatment as a result of the reduction in the efficacy of the partner drug. However, a larger fraction of consumers choose to substitute away from the ACT in favor of the partner drug as a result of the reduction in the efficacy of the ACT.

In one sense, a comparison of outcomes in region A and region B suggests that a ban on artemisinin monotherapy use—if feasible—may be a beneficial, though clearly second-best, policy instrument. The policy preserves the efficacy of artemisinin by increasing the use of ACTs. Yet, because the fraction of the population that goes without treatment is almost identical between regions, the ban does not significantly increase disease transmission. As reported in table 4, external

costs associated with mortality and morbidity in region B are approximately $15.7 billion. Thus, although only 64 percent of the global population live in region B, the region generates only 59 percent of global external costs.

The distribution of consumer surplus between regions elucidates some of the downsides associated with the ban. Consumer surplus in region B amounts to only 57.5 percent, or $2.5 billion, of global consumer surplus, and only 36 percent of global surplus associated with purchases at the drug shop. As a result of the ban, households that would prefer the artemisinin monotherapy in an unregulated environment, but use the ACT due to the ban, are forced to spend a greater share of their income on malaria treatment than desired. Households that receive the partner drug are left with a product of lower efficacy than desired. Because the magnitude of external costs dwarfs the surplus gains from consuming anti-malarials, the benefits of the monotherapy ban outweigh these losses. One major caveat in this discussion is that the geographic spread of parasite strains represent a spatial externality. The ban on artemisinin monotherapies in region B partially preserves the efficacy of artemisinin monotherapies in region A. The magnitude of these externalities is not evaluated here.[15] Moreover, this discussion is subject to a number of caveats, which will be discussed in the conclusion. Under the first scenario, global donor and taxpayer outlays amount to $2.7 billion. Producers of *artemisia annua* receive $1 billion in surplus. Welfare is approximately -$24 billion.[16] Having discussed outcomes under scenario one in which all artemisinin for ACTs and artemisinin monotherapies is plant-derived, I now turn to the introduction of semi-sytnethic artemisinin in scenario two.

Scenario Two: Semi-synthetic technology is introduced.

A comparison of first-period outcomes for region A in table 3 under scenario two with those in scenario one shows that price reductions associated with semi-synthetic technology pull a large share of consumers away from the public clinic in favor of the local drug shop. In scenario one 40 percent of the infected population of region A attended the clinic. In scenario two, only 33 percent attend the clinic. The remaining seven percent of infected individuals that attended public clinic

[15] One could use this model to evaluate the effects of the ban on artemisinin monotherapies by comparing the outcomes of two scenarios: the first in which both regions allow the use of artemisinin monotherapies, the second in which region B bans monotherapies.

[16] Because I include the concepts of producer and consumer surplus in my calculations of total welfare, these estimates are substantially below previous estimates of the economic costs of malaria. If consumer and producer surplus are excluded from the calculations, estimates are comparable to previous studies.

in scenario one now purchase at the local drug shop because travel costs remain unchanged while the cost of the ACT at the local drug shop declines. The composition of local shop drug sales is dramatically different in scenario two. The share of individuals purchasing the ACT increases from 0.04 to 0.28. Thus, the total share of the population receiving the ACT increases from 0.44 to 0.61. In contrast, even though the price of the artemisinin monotherapy falls, the share of individuals that purchase the artemisinin monotherapy decreases from 0.18 to 0.03. A comparison of the initial period outcomes in figures 9 and 11 explains this outcome. The introduction of semi-synthetic technology causes consumers at the local drug shop to substitute towards the higher efficacy product. The reduction in the price of artemisinin monotherapies crowds out a portion of partner drug consumption. Because the price of the partner drug is unaffected by the introduction of semi-synthetic artemisinin, the share of individuals that goes without treatment is unchanged.

[Figure 11 about here.]

The introduction of semi-synthetic artemisinin also has a dramatic impact on the dynamics of consumption patterns and drug efficacy. Because pharmaceutical supply curves are more elastic in this scenario, consumption is more responsive to changes in efficacy. ACTs and artemisinin monotherapies displace the partner drug in early periods. Accordingly, fitness costs outweigh the evolutionary pressure to maintain resistance to the partner drug. These improvements in the effectiveness of the partner drug dramatically increases its consumption share. By the fourth year, consumption of the partner drug is higher than in scenario one. Over time, households also substitute away from the ACT at the local drug shop in favor of the artemisinin monotherapy or treatment at the clinic.

As reported in table 3, only 1 percent of housheolds purchase the ACT at the local drug shop by the seventh year. The share of individuals that travel to the clinic is 0.34, compared to 0.38 in the first scenario. Thus, the share of individuals that receive the ACT by the final period falls by 0.04 relative to scenario one. Demand for the lower-efficacy drugs both increase over time. By the seventh period, the share of individuals that purchase the artemisinin monotherapy is equivalent to scenario one. The share treated with the partner drug increases to 0.22. The total share of the population that receives some form of treatment is 0.74, equivalent to scenario one. As shown in figure 10, the final efficacy of the ACT is 0.80. Artemisinin monotherapies efficacy falls to 0.75.

The partner drug is 46 percent effective.

The total surplus of individuals attending the public clinic falls from $1.5 billion in scenario one to $1.2 in scenario two. Two main factors contribute to this welfare outcome. First, the reduction in the price of ACTs resulting from the introduction of semi-synthetic artemisinin induces a large share of households to purchase at the drug shop rather than attend the clinic. Second, increases in the use of anti-malarials reduces the efficacy of ACTs relative to scenario one. The total welfare of individuals who purchase at the local drug shop increases from $345 million in scenario one to $690 million. The factors contributing to this outcome are the mirror image of those that lead to the reduction in surplus at the public clinic. Additionally, the increase in the efficacy of the partner drug resulting from increased consumption of artemisinin derivatives leads to substantial gains in later periods. The introduction of semi-synthetic artemisinin increases total consumer surplus by $75 million. External costs associated with mortality and morbidity are $9.4 billion compared to $10.8 in scenario one. Thus, total welfare in the region increases by $ 1.5 billion from -$9 billion in scenario one to -$7.5 billion.

The impacts of semi-synthetic artemisinin in region B are qualitatively similar to those in region A. In the first period, the reduction in the price of ACTs induces an additional 8 percent of the infected population to purchase the ACT at the local drug shop. Approximately half of these individuals purchased the partner drug in scenario one. The other half traveled to the clinic. The share of the population receiving ACT increases from 0.59 in scenario one to 0.63 in scenario two. The efficacy of ACTs and artemisinin monotherapies decreases faster in scenario two than in scenario one. By the seventh year ACTs are 79 percent effective. Artemisinin monotherapies are 77 percent effective. As in region A, the ACT initially displaces the partner drug. Accordingly, the efficacy of the partner drug initially increases relative to first-period levels. The increase in partner drug efficacy amidst declines in the efficacy of ACTs and artemisinin monotherapies induces a growing share of consumers to substitute towards the partner drug. By the seventh year, the effectiveness of the partner drug falls to 0.42.

Consumer surplus associated with the clinic in region B decreases from approximately $2.3 billion in scenario one to $2.1 billion in scenario two. Surplus for individuals who purchased at the local drug shop increases from $195 million to $484 million. On net, consumers in region B gain $17.8 as a result of the technology. Morbidity and mortality costs in region B decrease by only $57

million from scenario one to scenario two. Total welfare in the region increases by $210 million from -$13.3 billion in scenario one to -$13.1 billion in scenario two.

A comparison of outcomes in regions A and B under scenario two suggests that the benefits of a ban on artemisinin monotherapies decreases when semi-synthetic artemisinin is introduced. On one hand, the share of global consumer surplus generated in region B increases from 57.5 percent in scenario one to 63.8 percent in scenario two. On the other hand, the share of the global externality generated in the region B increases from 59 percent in scenario one to 62.5 percent in scenario two. As a share of welfare costs associated with malaria, region B increases from 60 percent in scenario one to 63 percent in scenario two. The effects of semi-synthetic technology on consumption patterns in region A explain this result. Comparing figures 9 and 11, it becomes apparent that, when the technology is introduced, ACT consumption crowds out a portion of the demand for artemisinin monotherapies in region A. Consumption patterns across treatments bear a greater resemblance to those in region B. The loss in consumer surplus associated with a ban on artemisinin monotherapies diminish in region B. At the same time, the externalities associated with artemisinin monotherapy use in region A decrease.

Producer surplus for farmers falls from $1,053 million in scenario one to $409.9 million in scenario two because less plant-derived artemisinin is produced. Lower priced ACTs and lower public clinic attended reduce the burden on donors and taxpayers falls from $2.7 billion in scenario one to $1.7 in scenario two. The global malaria burden falls from -$23.9 billion in scenario one to -$21.9 billion in scenario two.

Policy Implications and Conclusion

This research integrates a mathematical epidemiology model of malaria transmission and drug resistance adapted to account for the geographic spread of resistance into a dynamic, partial equilibrium two-region trade framework representing the market for anti-malarials to investigate the potential economic and public health effects resulting from the introduction of semi-synthetic artemisinin. I find that the technology leads to a present-value gain of approximately $2 billion over a seven-year time horizon. Losses in surplus for growers of *artemisia annua* are more than offset by gains to infected individuals, donors and taxpayers, and society at large. Increased global access to ACTs

reduces the external costs associated with mortality and morbidity by $1.5 billion.

Dividing malaria-endemic countries by treatment policy highlights the bluntness of an outright ban on monotherapies. Semi-synthetic ACTs displace artemisinin monotherapies. When semi-synthetics are introduced, regions that have banned artemisinin monotherapies account for a greater per-capita share of the welfare losses associated with malaria than regions without a ban. However, these findings do not suggest that these markets should be left unregulated. As shown in table 4, external costs of malaria transmission and drug resistance dwarf the direct gains to individual consumers and international donors. A more subtle policy which induces infected individuals to seek more effective treatment is needed. Until recently, the international community provided indirect subsidies targeted at ACT producers and distributors under the Affordable Medicines Facility. Some have deemed these efforts a failure because there is little evidence these subsidies reached end users (Cohen et al., 2015).

Because semi-synthetic production technology affects the availability and usage of all anti-malarial drugs, it presents a feasible "second-best" policy instrument. A restriction on the production of semi-synthetic artemisinin increases the price of ACTs and artemisinin monotherapies. This *de facto* tax can be used to manage negative externalities associated with drug resistance. Conversely, production of semi-synthetic ACTs at greater than *laissez faire* levels lowers the price of artemisinin-based anti-malarials, and can be used to reinforce positive externalities associated with reductions in malaria transmission via increased drug consumption. The rollout of semi-synthetic artemisinin through a dynamic production quota to significantly could significantly enhance welfare outcomes. If coupled with a consumer-oriented subsidy on ACTs, policymakers could reach optimal levels.

I conclude with a final note of caution. My results are contingent upon a large set of parameter calibrations and a number of underlying assumptions regarding the distribution of consumers in terms of economic distance to clinics and willingness and ability to pay for anti-malarials. Though findings appear reasonable, alternative specifications or assumptions may alter the outcomes discussed above.

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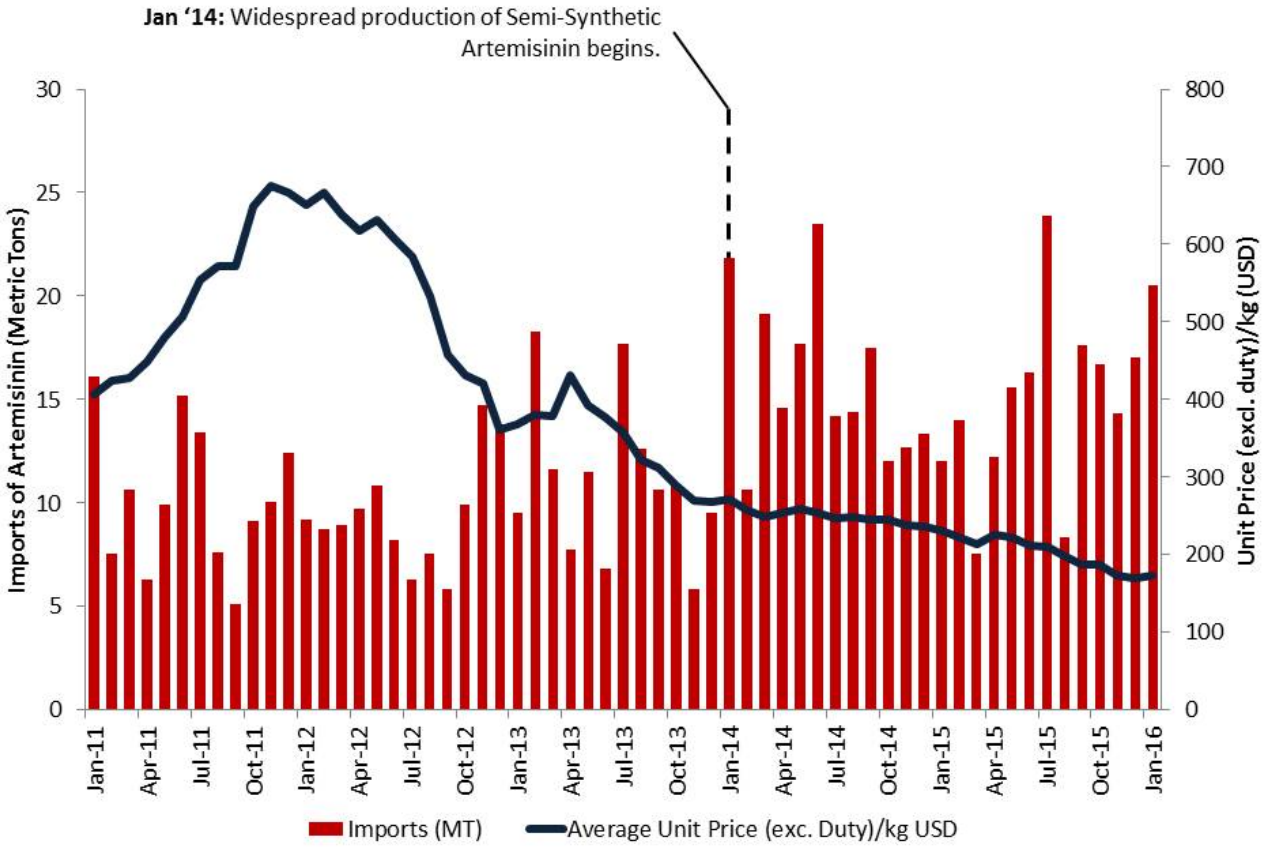
Figure 1: Monthly Imports of Artemisinin into India, Jan 2011 - Jan 2016



Data Source: A2S2 Assured Artemisinin Supply System. www.a2s2.org.

Figure 2: The Effects of Introducing Semi-Synthetic ACT Technology

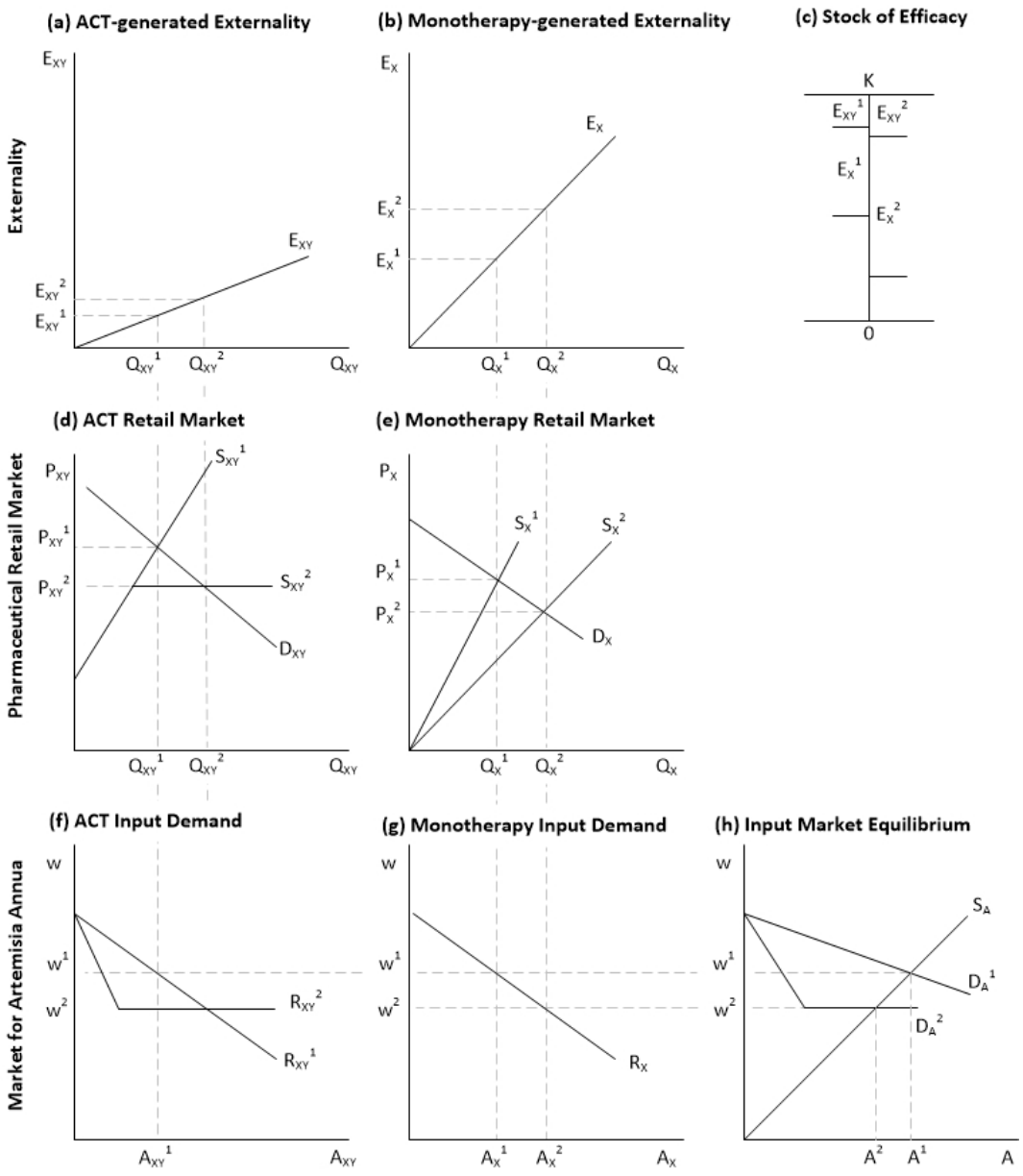


Figure 3: Schematic Diagram of Epidemiological-Economic Framework

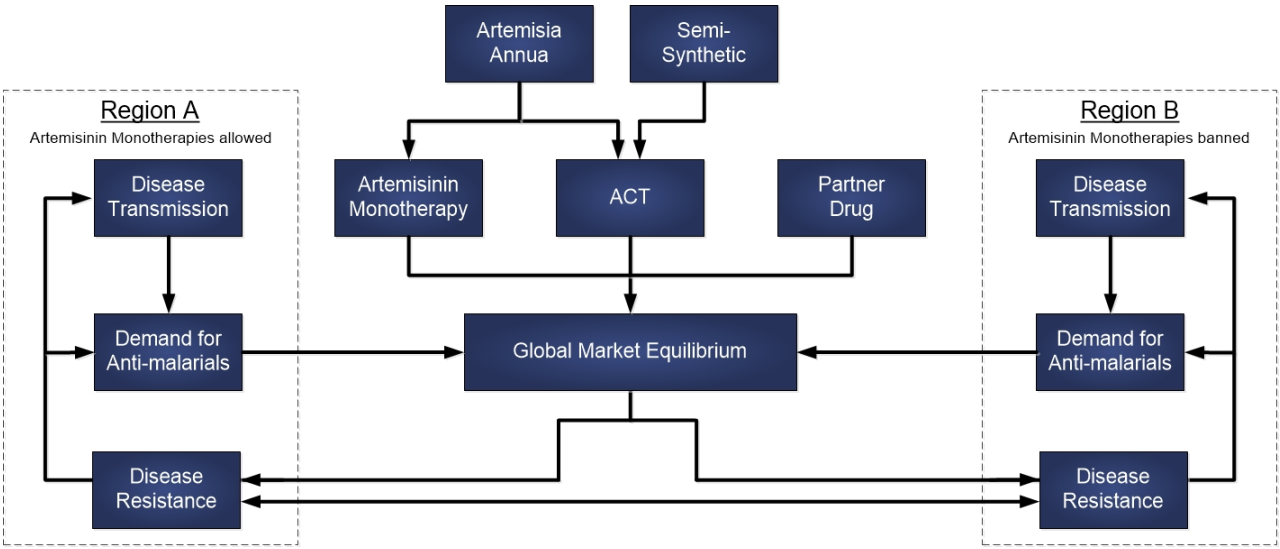
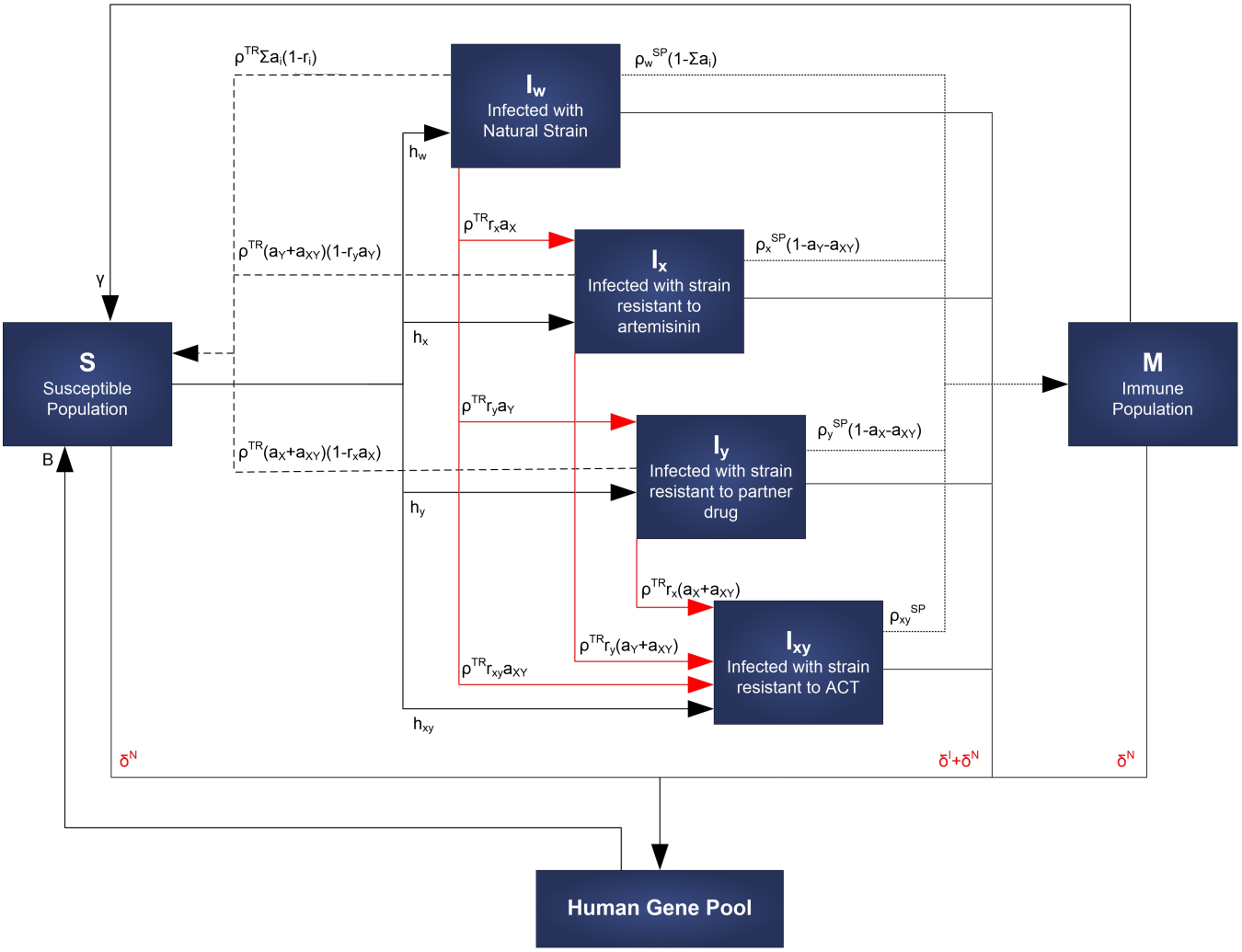


Figure 4: Schematic Representation of Epidemiological Equations of Motion within a Region



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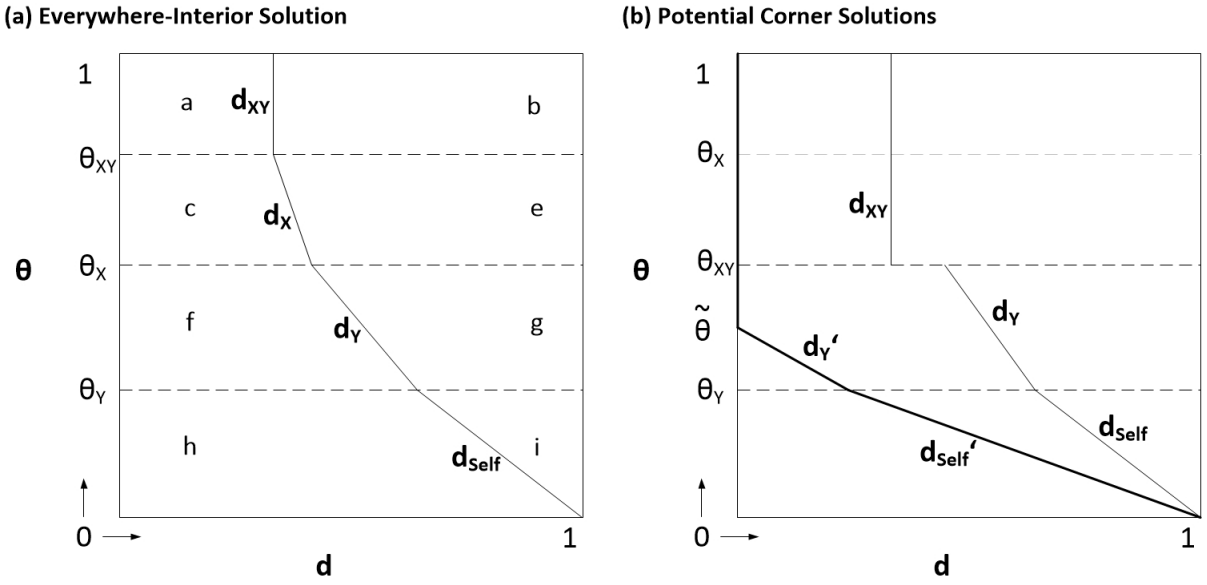
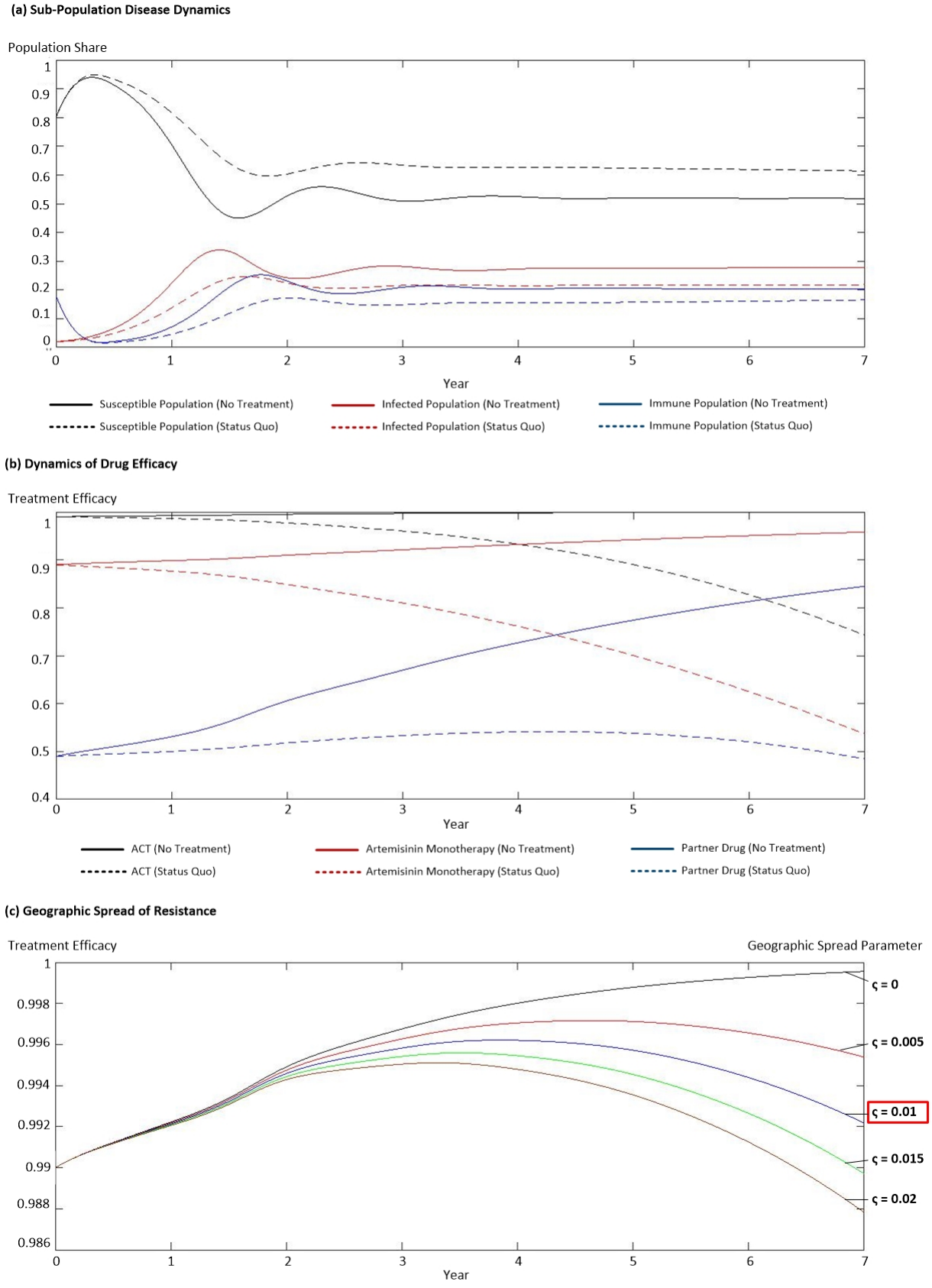


Figure 6: Calibrated Epidemiological Framework Under Alternative Treatment Scenarios



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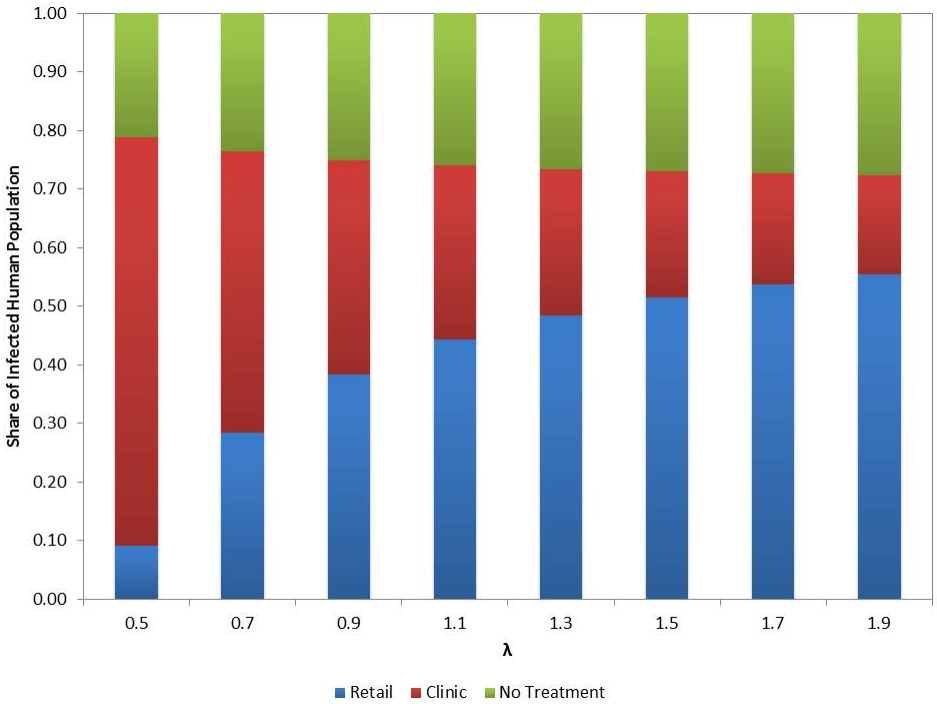

Figure 8: Global Demand for Anti-Malarials

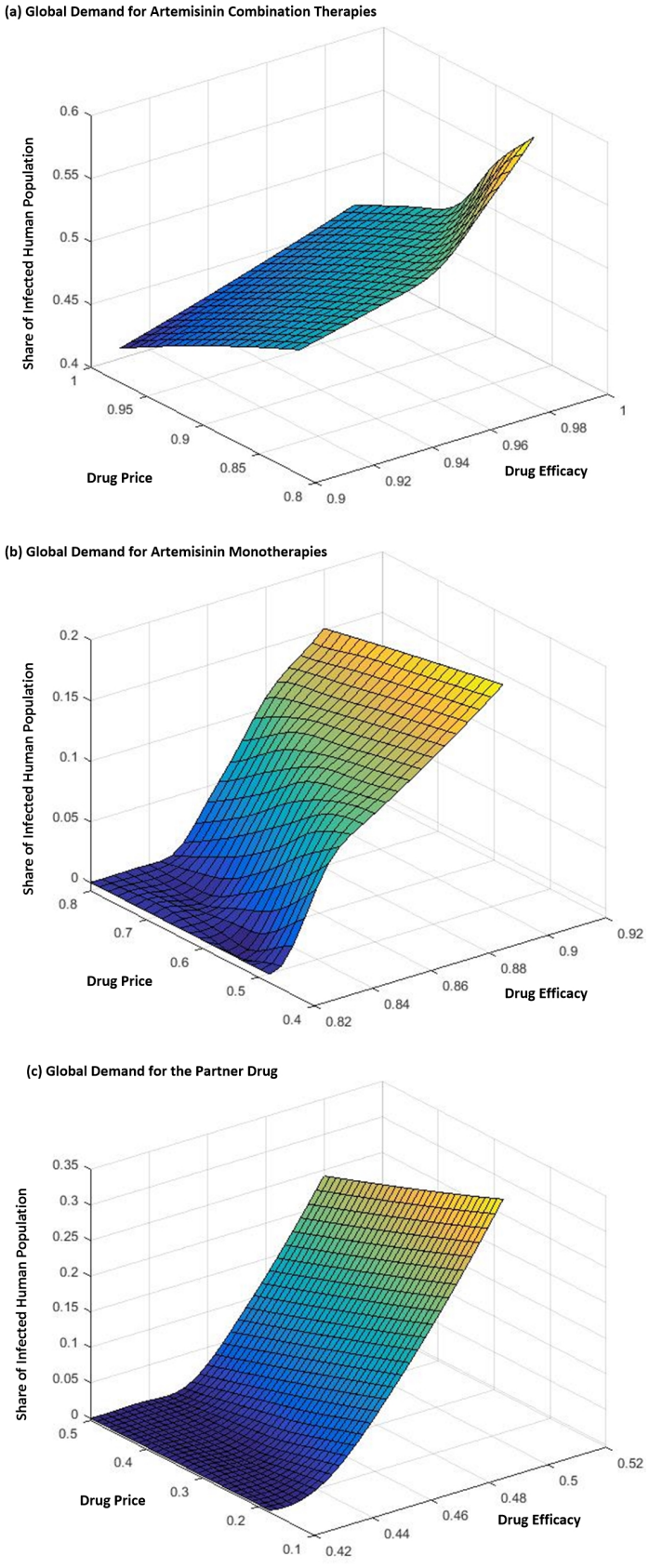

Figure 9: Drug Consumption Under Traditional Production Scenario

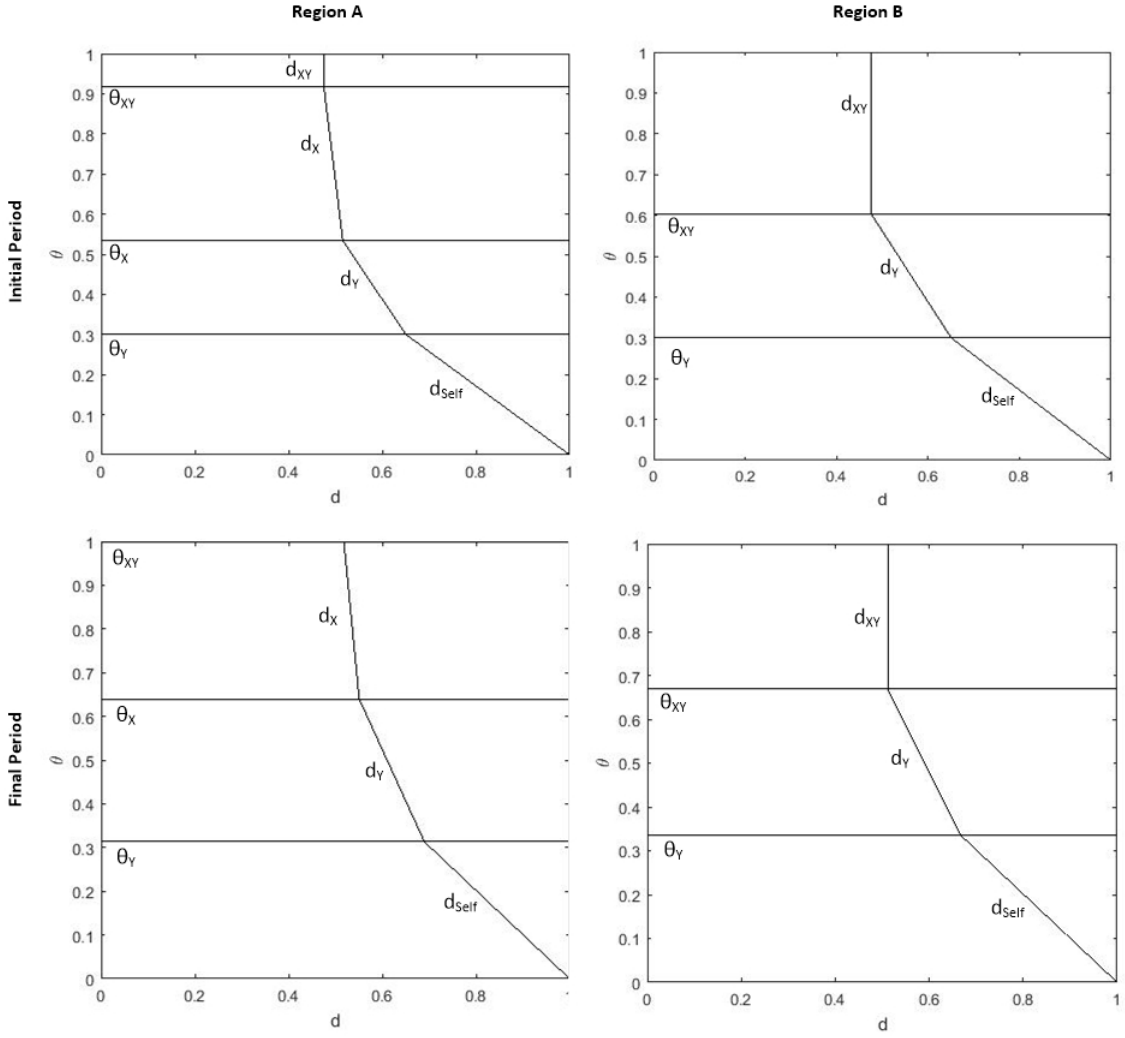

Figure 10: The Dynamics of Treatment Efficacy

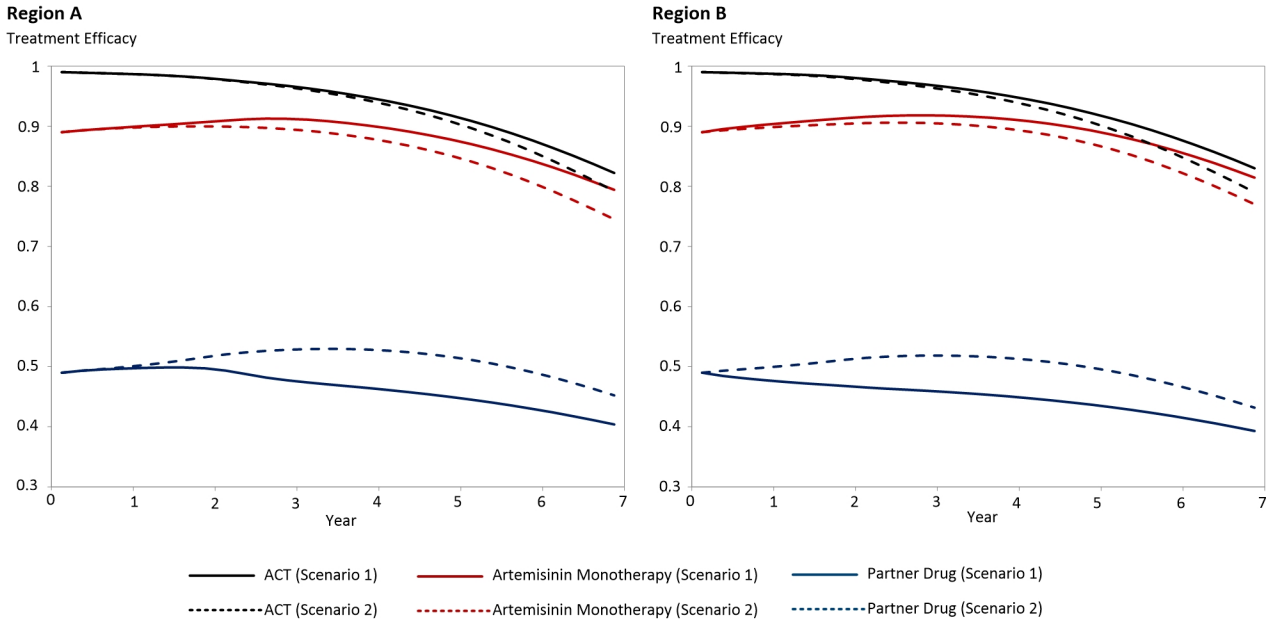

Figure 11: Drug Consumption Under Semi-Synthetic Production Scenario

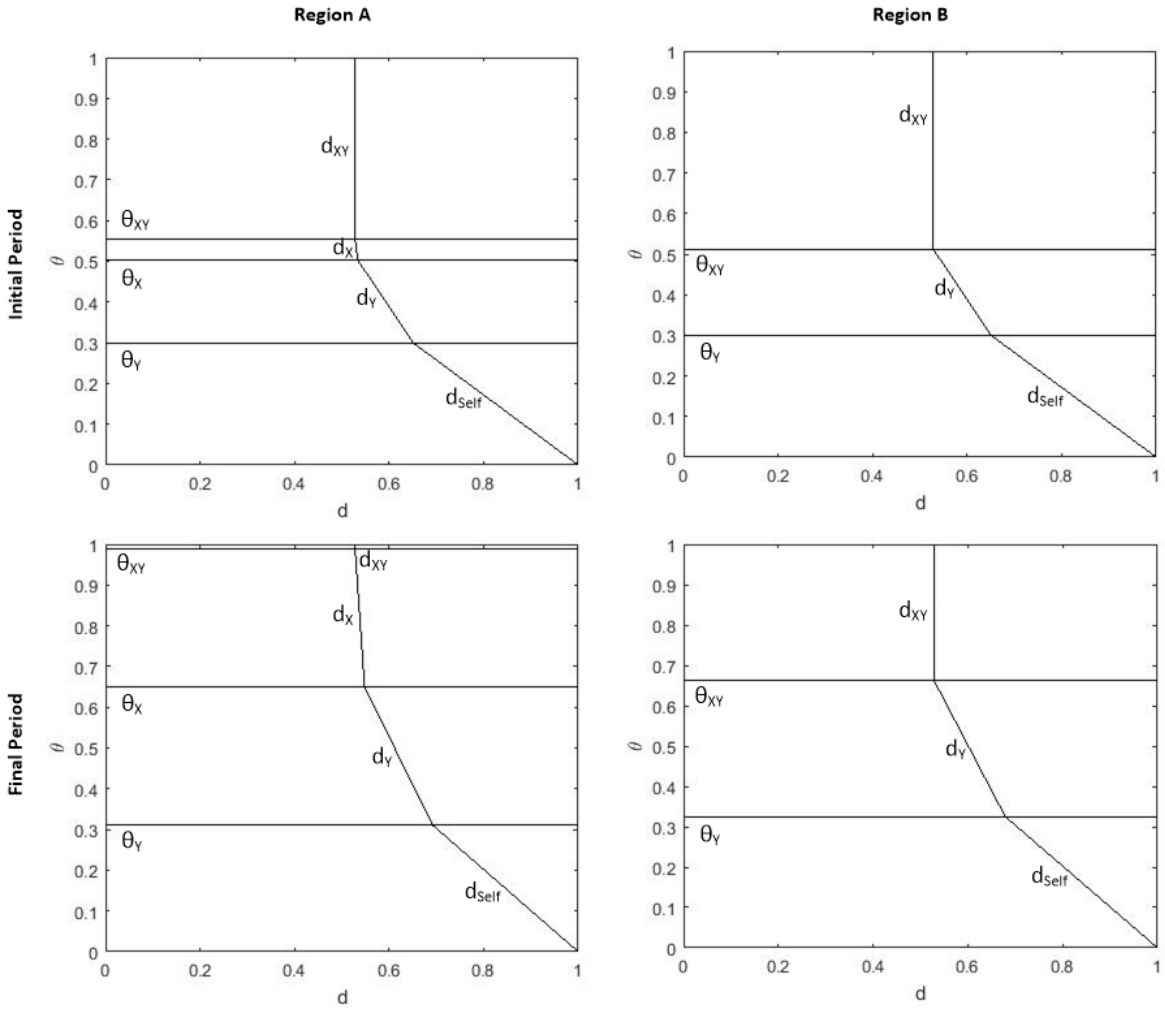

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Table 1: The Global Malaria Burden, 2013

	Population *(millions)*	Estimated Cases *(thousands)*	Estimated Deaths
Africa	923	163,000	528,000
Eastern Mediterranean	426	9,000	11,000
Europe	131	2	0
Americas	574	700	800
South-East Asia	1,855	24,000	41,000
Western Pacific	1,685	1,000	3,300
Total	5,594	198,000	584,000

Data Source: WHO (2014)

Table 2: Calibration of Epidemiological Parameters from Laxminarayan et al. (2010)

Parameter Name	**Calibrated Value**	**Description**
f	2.7	Quarterly biting rate
b_1	0.5	Transmission efficiency from infected human to mosquitoes
b_2	0.8	Transmission efficiency from infected mosquitoes to humans
τ	0.11	Incubation period (10 days)
m	180	Mosquito density
δ_{mos}	8.1	Expected daily biting rate is 10 days
ρ_w^{sp}	$5 * 10^{-6}$	Baseline recovery rate for wild type infection
ρ_x^{sp}	1.2*ρ_w^{sp}	Baseline recovery rate for infections resistant to X
ρ_y^{sp}	1.2*ρ_w^{sp}	Baseline recovery rate for infections resistant to Y
$\rho_x y^{sp}$	$1.4\rho_w^{sp}$	Baseline recovery rate for infections resistant to XY
ρ^{tr}	9	Individuals stop being infectious after one treatment day
T	1.11	Immunity duration without biting (100 days)
δ_{inf}	0.75	Malaria related mortality rate
δ_n	0.63	Average life expectancy is 45 years
r_y	10^{-7}	Rate of spontaneous resistance to Y
r_x	10^{-9}	Rate of spontaneous resistance to X
$r_x y$	$r_x * r_y$	Rate of spontaneous resistance to XY

Table 3: Share of the Infected Human Population by Choice of Treatment

		Year *(first quarter)*						
		1	2	3	4	5	6	7
Scenario 1: Traditional Production	**Region A**							
	Clinic	0.40	0.40	0.41	0.41	0.40	0.39	0.38
	Retail							
	ACT	0.04	0.03	0.02	0.01	0.00	0.00	0.00
	Art Mono	0.18	0.18	0.19	0.18	0.17	0.17	0.17
	Partner	0.13	0.13	0.15	0.16	0.17	0.17	0.19
	Total Retail	0.35	0.34	0.36	0.35	0.34	0.34	0.36
	Total Treated	0.75	0.74	0.77	0.76	0.74	0.73	0.74
	Total ACT	0.44	0.43	0.43	0.42	0.40	0.39	0.38
	No Treatment	0.25	0.26	0.23	0.24	0.26	0.27	0.26
	Region B							
	Clinic	0.42	0.41	0.39	0.37	0.35	0.34	0.33
	Retail							
	ACT	0.18	0.17	0.17	0.16	0.15	0.15	0.14
	Art Mono	-	-	-	-	-	-	-
	Partner	0.16	0.17	0.20	0.22	0.23	0.25	0.26
	Total Retail	0.34	0.34	0.37	0.38	0.38	0.40	0.40
	Total Treated	0.75	0.75	0.76	0.75	0.73	0.74	0.73
	Total ACT	0.59	0.58	0.56	0.53	0.50	0.49	0.48
	No Treatment	0.25	0.25	0.24	0.25	0.27	0.26	0.27
Scenario 2: Semi-Synthetic Production	**Region A**							
	Clinic	0.33	0.36	0.35	0.34	0.33	0.33	0.34
	Retail							
	ACT	0.28	0.23	0.19	0.14	0.10	0.05	0.01
	Art Mono	0.03	0.03	0.06	0.10	0.13	0.16	0.17
	Partner	0.11	0.12	0.15	0.17	0.18	0.20	0.22
	Total Retail	0.42	0.38	0.39	0.40	0.41	0.40	0.40
	Total Treated	0.75	0.75	0.74	0.74	0.74	0.74	0.74
	Total ACT	0.61	0.59	0.53	0.48	0.43	0.39	0.34
	No Treatment	0.25	0.25	0.26	0.26	0.26	0.26	0.26
	Region B							
	Clinic	0.37	0.36	0.35	0.35	0.35	0.35	0.34
	Retail							
	ACT	0.26	0.25	0.24	0.23	0.21	0.20	0.19
	Art Mono	-	-	-	-	-	-	-
	Partner	0.12	0.13	0.15	0.17	0.18	0.19	0.21
	Total Retail	0.38	0.38	0.39	0.40	0.40	0.39	0.40
	Total Treated	0.75	0.75	0.74	0.74	0.74	0.74	0.76
	Total ACT	0.63	0.62	0.59	0.57	0.56	0.55	0.53
	No Treatment	0.25	0.25	0.26	0.26	0.26	0.26	0.26

Table 4: Present Value Social Welfare Outcomes *(Millions of Dollars)*

	Scenario 1			Scenario 2			% Change
	Region A	Region B	**Total**	Region A	Region B	**Total**	in Total
Consumer Surplus							
Clinic	1,475	2,263	3,738	1,205	2,126	3,332	-10.9
Retail	345	195	540	690	485	1,175	117.5
Total	1,820	2,458	4,278	1,895	2,611	4,506	5.3
Producer Surplus			1,053			410	-61.1
Donor & Taxpayer Outlays			-2,728			-1,745	36.0
Mortality & Morbidity	-10,780	-15,720	-26,500	-9,398	-15,663	-25,061	5.4
Total	-8,960	-13,262	-23,896	-7,503	-13,052	-21,890	8.4