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

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Abstract

Anti-malarial drug use generates both positive externalities—by reducing disease transmission—and negative externalities—by increasing antimicrobial resistance. In any given country, the size of these externalities depends on a number of factors, including drug coverage and the prevalence of disease. In this paper, I analyze the economic impact of a new, semi-synthetic production technology by which to derive artemisinin for use in artemisinin-based combination therapies (ACTs). I show that the introduction of this technology will reduce the absolute price of all anti-malarials, and thereby increase the positive externality related to disease transmission. However, the technology will also reduce the relative price of monotherapy drugs, which generate a greater negative externality associated with drug resistance. To quantify the overall effect of semi-synthetic artemisinin on global welfare, I integrate a microbiological-epidemiological model of malaria transmission and drug resistance into a partial equilibrium model depicting the supply and demand for anti-malarials across 93 malaria-endemic countries. This specification allows me to account for differences in treatment policy, the rate of transmission, and resistance patterns across countries. I find that the net externality generated by the introduction of semi-synthetic artemisinin is overwhelmingly positive. The technology will ease donor financing costs and economic losses associated with mortality and morbidity by between $945 million and $2.1 billion over the next 15 years.

Key words

Biotechnology, Disease Transmission, Antimicrobial Resistance, Malaria, Artemisinin
Introduction

In this paper I quantify the economic and public health impact of a new, semi-synthetic production technology by which to derive artemisinin for use in artemisinin-based combination therapies (ACTs) used to treat malaria. Semi-synthetic artemisinin was designed to increase access to ACTs, lower prices, and reduce donor financing costs by removing plant-based chemicals from the production process. The introduction of this technology will affect the availability and usage of a broader range of anti-malarial drugs through consumer price-seeking behavior and changes in related input markets. I integrate a microbiological-epidemiological model of malaria transmission and drug resistance, adapted to account for the spread of infection across countries, with an economic model of the global market for anti-malarials to analyze the dynamic implications of this price shock on externalities related to disease transmission and drug resistance.

Anti-malarial drug use generates both positive and negative externalities. Successful drug use generates a positive externality by reducing the transmission of infections. In addition to curing the treated individual, drug use eliminates all future infections that would have resulted from the original host. Alongside the positive transmission externality, consumption of anti-malarials generates a negative externality associated with drug resistance. When parasites develop resistance in response to drug use, future treatments become less efficacious. The rate at which drug resistance develops depends on the chemical composition of the anti-malarial. ACTs combine artemisinin with another active ingredient to increase efficacy and prolong the useful life of the drug. The presence of the partner ingredient slows the development of resistance because parasites must mutate in a way that is simultaneously resistant to two active ingredients. In many countries, however, ACTs are marketed alongside artemisinin monotherapies. The consumption of artemisinin as a monotherapy hastens resistance to artemisinin both as a monotherapy and in ACT form.

This externality is especially critical given the high rate of reproduction for malaria. Some estimates of the basic reproductive number for malaria, which represents the number of additional infections that arise as a result of each new infection, are as high as 3,000 (Smith et al., 2007).
In any given country, the marginal external cost (or benefit) resulting from a price reduction depends on a number of factors, including current levels of endemicity and drug coverage. Malaria is endemic across 97 countries and remains a risk for almost half of the global population. The disease is most heavily concentrated in sub-Saharan Africa, due in part to high infection rates among small children. If disease prevalence and transmission are minimal, parasites are slow to develop resistance and the associated externality is small. Many countries have implemented policies that affect the level of drug coverage, such as the heavy subsidization of ACTs and restrictions on the use of monotherapies that affect the level of drug coverage. If drug coverage is high, a decrease in prices will have an insignificant impact on treatment levels and the transmission externality.

However, countries and their policy choices do not exist in a vacuum. Transmission and resistance externalities are global in scope. Infections and drug resistance acquired in one area can spread to other areas through human and entomological migration. The precise mechanism for this geographic spread is not well understood, but its existence is well-documented, especially in the context of anti-malarial resistance. 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 burden of the disease (Lubell et al., 2014).

Artemisinin has traditionally been derived from a plant called *artemisia annua*. However, researchers recently developed a method by which to produce artemisinic acid for use in ACTs semi-synthetically using a genetically engineered production technology. Before introducing my integrative assessment model, I use a simple, static framework to show that the technological change affects drug prices in two ways. First, the introduction of semi-synthetic artemisinin lowers the absolute price of both ACTs and artemisinin monotherapies. This price reduction increases drug coverage and thereby increases the positive externality as-

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2For example, resistance to chloroquine—an anti-malarial drug previously recommended by World Health Organization (WHO) as 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 America in the 1960s and 1970s. Today chloroquine remains effective in only a few Latin American countries.
associated with disease transmission. Second, semi-synthetic artemisinin lowers the relative price of artemisinin monotherapies. The change in relative prices induces some consumers to substitute away from ACTs in favor of monotherapies. Increased monotherapy consumption increases the negative externality associated with drug resistance, which could dampen (or even reverse) the potential benefits of the technology.

I develop an integrative assessment model that incorporates an epidemiological representation of the spread of malaria and the evolution of drug resistance with an economic model of anti-malarial production and consumer price-seeking behavior to analyze the impact of introducing semi-synthetic artemisinin on welfare outcomes. This framework extends existing models in three ways. First, I use a global trade model that allows me to account for differences in treatment policy, transmission rates, and resistance patterns across countries. Second, my representation of drug demand allows me to characterize the simultaneous trade-off between seeking treatment at a public health clinic versus purchasing an anti-malarial at the local drug shop under various policy environments. Finally, I use gravity-based measures of bilateral linkedness to estimate the rate at which infections spread from one country to another.

I find that the benefits of semi-synthetic artemisinin associated with long-run reductions in mortality, morbidity, and donor financing costs outweigh the costs of increased resistance. The introduction of semi-synthetic artemisinin decreases the economic cost of malaria by between $63 million and $145 million per year, or between $945 million and $2.1 billion over a 15 year time horizon. When the supply of the agricultural input is less than perfectly elastic, some of these savings are offset by losses in surplus for farmers. The net result is a 1.4% to 1.7% reduction in global infections and a $495 million to $2.1 billion increase in global social welfare over the next 15 years. Countries in low transmission areas and countries in which ACTs are subsidized in the public sector are the primary beneficiaries of the technology. On average, semi-synthetic artemisinin increases welfare in those areas by 3.55 and 2.38 percent, respectively.
Artemisinin-Based Anti-Malarials

For the past two decades artemisinin and its derivatives have been the most effective and fastest acting among all current anti-malarial treatments worldwide. Access to ACTs has contributed to a 47 percent reduction in malaria-related mortality between 2000 and 2013 from 1.1 million deaths in 2000 to 584,000 deaths in 2013 (WHO, 2014). However, efficacious treatment may soon become infeasible. Past drug consumption and a variety of other conditions have led to antimicrobial resistance to ACTs in at least five South-East Asian countries. Recent epidemiological evidence suggests that the prevalence and geographic spread of resistance may be greater than previously believed (Tun et al., 2015). Mutations in the 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).

**Policy Environment.** Governments and inter-governmental agencies have proposed two types of treatment policies to increase access to ACTs and delay the onset of drug resistance. The first policy is the heavy subsidization of ACTs in public health clinics. Many countries, especially in sub-Saharan Africa, provide ACTs for free or at very low prices to patients in public health facilities. These policies are costly to international donors, and even in the presence of public-sector subsidies ACT access remains low among many populations. Less than 20 percent of malarial children in sub-Saharan Africa received ACT treatment in 2013 (WHO, 2014). People from remote areas often incur significant travel expenses to attend the nearest public health clinic and, upon arrival, patients may be forced to wait for hours before diagnosis due to over-crowding and poor clinic staffing. As a result of these barriers, many people go untreated or seek treatment with private vendors where ACTs may be more expensive. The retail sector accounts for 40 to 97 percent of anti-malarial sales (Arnold et al., 2012).³

³A small number of countries offer private-sector subsidies for ACTs under the Affordable Medicines Facility for malaria (AMFm). Under this program, subsidies are provided directly to ACT manufacturers. Evidence in the economics literature suggests these interventions have had minimal success in reaching the end user (Cohen et al., 2013; Cohen, Dupas and Schaner, 2015)
A second policy instrument targeting ACT access and drug resistance is the prohibition of artemisinin monotherapies. In 2007, the World Health Assembly adopted a resolution supporting monotherapy bans (WHO, 2014). Many countries have complied with this resolution by prohibiting the sale of artemisinin monotherapies in the private sector. Such a blunt policy instrument has several drawbacks. As intended, some individuals who would have purchased a monotherapy in the absence of a ban substitute in favor of the ACT as a result of the policy. Substitution of this form will delay resistance. There is also an unintended consequence. A portion of individuals who would have purchased the monotherapy in the absence of the policy choose not to purchase the ACT and will instead go untreated. A monotherapy ban eliminates the positive transmission externality that would have been associated with these individuals receiving a monotherapy treatment.\(^4\) Table 1 shows the international adoption of monotherapy bans and public-sector ACT subsidies from 2000 to

\(^4\)In reality, the imposition of a monotherapy ban may not completely eliminate monotherapy consumption. 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 officially banned (White, 2013). The purchase and sale of low quality anti-malarials in the informal private sector can be difficult to regulate for countries with poor institutional capacity (Björkman-Nyqvist, Svensson and Yanagizawa, 2012). If monotherapies consumption is not completely eliminated, a ban is less effective in delaying drug resistance, but the unintended consequences associated with foregone treatment are dampened.

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Table 1: Adoption of Monotherapy Bans and Public-Sector ACT Subsidies (Running Total)

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| Public-Sector ACT Subsidies | W Pacific | 1    | 1    | 1    | 3    | 3    | 4    | 5    | 5    | 6    | 7    | 8    | 8    | 8    | 8    | 8    |
|                            | SE Asia   | 0    | 1    | 1    | 2    | 3    | 3    | 6    | 8    | 8    | 8    | 8    | 8    | 8    | 8    | 8    |
|                            | Americas  | 0    | 0    | 0    | 1    | 3    | 6    | 7    | 7    | 8    | 8    | 9    | 10   | 11   | 11   | 11   |
|                            | European  | 0    | 0    | 0    | 0    | 1    | 1    | 1    | 1    | 3    | 3    | 3    | 3    | 3    | 3    | 3    |
|                            | E Med.    | 0    | 0    | 0    | 1    | 1    | 3    | 4    | 5    | 5    | 7    | 7    | 7    | 7    | 7    | 7    |
|                            | African   | 0    | 1    | 1    | 4    | 5    | 8    | 15   | 18   | 21   | 27   | 32   | 33   | 34   | 35   | 35   |
| Total                      |           | 1    | 3    | 3    | 11   | 16   | 25   | 38   | 44   | 49   | 60   | 67   | 69   | 71   | 72   | 72   | 72   |

Data underlying this table are taken from the World Malaria Reports 2005 and 2008–2015.
2014. As of 2014, 72 countries subsidize ACTs for infected people who attend public clinics. Monotherapy bans have been implemented in 79 countries.

**Production.** Since the WHO recommended ACTs as the first-line malaria treatment policy in 2002, the market has expanded dramatically. Between 2005 and 2013 production increased from 11 million to over 390 million treatments worldwide (WHO, 2014). 79 malaria-endemic countries have adopted ACTs as the national first-line treatment strategy WHO (2014). A few ACT formulations dominate global usage. The two most common formulations—artemether-lumefantrine and artesunate plus amodiaquine—represent a combined 99 percent of ACT production (WHO, 2014). Eleven pharmaceutical companies manufacture ACTs, and the two largest manufacturers—Novartis Pharmaceuticals and Sanofi—provide the medicines at cost to developing countries.

Artemisinin has traditionally been derived from the leaves of a shrub grown primarily in central China and Vietnam, known as *artemisia annua*. After harvest, the dried leaves are collected and sent for chemical extraction. Per hectare yields are heavily dependent on rainfall, climate, and other environmental factors (Shretta and Yadav, 2012). Due to the rapid increase in demand for ACTs and poor weather in Chongqing province in 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). Monthly prices of plant-derived artemisinin from January 2011 to January 2015 are reported in Figure 1. Following the initial adjustment phase from 2002 to 2012, the market for *artemisia annua* has adapted to the increase in demand through the use of fixed-price contracts and non-governmental demand forecasts. 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). One proposed

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5 Chloroquine is the first-line treatment in 10 Central American and Caribbean countries where it remains efficacious.
solution was bypassing agricultural processes by producing synthetic artemisinin. Synthetic technologies to produce artemisinin have been proposed since at least 1999 (Bouwmeester et al., 1999), but all methods of synthesis proved 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 in which the early stages of synthesis are accomplished via biological processes, and only the final stages involve organic chemistry (Padden et al., 2013). Semi-synthetically produced artemisinin is chemically indistinguishable from its plant-derived counterpart (Paddon and Keasling, 2014). 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, and by the end of the year, Sanofi produced 115 million semi-synthetic treatments, or approximately 50 percent of global ACT production (Palmer, 2014).
Literature Review

Volumes of microbiological and epidemiological research over many decades have analyzed the chemical properties of antimicrobials and their effects on resistance. In contrast, these issues have entered the economics literature relatively recently. This study relates to three distinct, but interconnected, strands on the economics of antimicrobials and infectious disease. The first strand integrates mathematical epidemiological models into an economic framework to determine the optimal usage of anti-microbials or assess the desirability of policy interventions to combat disease (Laxminarayan and Brown, 2001; Laxminarayan et al., 2010; Smith et al., 2005; Wilen and Msangi, 2003). Models of malaria transmission and drug resistance in this line of literature have become increasingly complex since the seminal work by Koella (1991), but the complexities of dynamic optimization often force the modeler to simplify production and individual decision making processes (Klein et al., 2007). Laxminarayan et al. (2010) is the most relevant analysis in this line of research. The authors investigate the effects of a global subsidy for 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 each drug is assumed to be fixed and independent of the quantity produced and consumed.

Another strand in the literature analyzes the effects of drug pricing policies on treatment decisions (Björkman-Nyqvist, Svensson and Yanagizawa, 2012; Cohen et al., 2013; Cohen, Dupas and Schaner, 2015). 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, Dupas and Schaner (2015) use an expected utility framework to assess whether a individuals 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 not modeled, but are discussed in passing.
Formal economic analyses of the anti-malarial drug supply are few. 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, Webster and Yadav (2014). The authors develop a stochastic framework to model the ACT supply chain to assess the effects of various policy interventions. However, the analysis ignores the interactions with related markets for artemisinin monotherapies and partner drugs.

**Market Effects of Semi-Synthetic Artemisinin: A Simple Static Framework**

Before embarking on the formal analysis, I illustrate the effects of introducing semi-synthetic artemisinin on market outcomes using a simple, static model. Figure 2 illustrates the global artemisinin supply chain from farm to end user. Panels (a) and (b) of the Figure 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 the first scenario, referred to throughout as the “traditional” scenario, artemisinin for use in monotherapies and ACTs is derived from *artemisia annua*. In the second scenario, a 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 derived demands $R_{XY}$ and $R_X$ for *artemisia annua* in panels (c) and (d). In scenario one, the market clears when the total quantity of *artemisia annua* demanded, $R_{XY}^1 + R_X = D_A$, is equal to the quantity supplied, $S_A$. Panel (e) depicts this equilibrium price at $w^1$. The amount of *artemisia annua* produced is $A^1$. Monotherapy producers use $A_X^1$ tons of *artemisia annua* to produce $Q_X^1$ monotherapy treatments, which are sold at price $P_X^1$. ACT producers use...
Figure 2: Marketwide Effects of Introducing Semi-Synthetic ACT Technology

I model the introduction of semi-synthetic technology in the second scenario as a constant marginal cost production activity, where \( S_{XY}^2 \) corresponds to a 10% cost savings relative to \( P_{XY}^1 \). The technology simultaneously pivots the derived demand for \textit{artemisia annua} for use in ACT production to \( R_{XY}^2 \). Total demand for \textit{artemisia annua} becomes \( D_A^2 \). This effect also pivots the monotherapy supply curve from \( S_X^1 \) to \( S_X^2 \) in panel (d). Again, the market clears where the demand for \textit{artemisia annua}, now \( D_A^2 \), is equal to the quantity supplied. The price of \textit{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 \( P_X^2 \). ACT producers use \( A^2 - A_X^2 \) tons of \textit{artemisia annua} to produce plant-derived ACTs. The remainder are produced 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 $Q_{XY}^2$.

A comparison of welfare under the two scenarios is ambiguous. As shown in Figure 2, semi-synthetic artemisinin affects both absolute and relative prices for ACTs and monotherapies. As a result of the reduction in absolute price levels, individuals who could not previously afford anti-malarials now have access to treatment. The corresponding increase in drug coverage will reduce disease transmission. At the same time, semi-synthetic artemisinin also affects the relative price of ACTs and monotherapies, resulting in an inverse Alchian-Allen effect (Alchian et al., 1967). Semi-synthetic production causes the price of the agricultural input to fall. Because the cost of transformation is higher for the ACT than for the monotherapy, the percentage reduction in the price of the monotherapy is greater than the percentage reduction in the price of the ACT. In other words, the price of the monotherapy falls relative to the price of the ACT. As a result, some people who purchased the ACT now purchase the monotherapy. This increase in the consumption of the monotherapy increases the resistance externality.

The supply elasticity of *artemisia annua* and the cross-price elasticity of demand for ACTs and artemisinin monotherapies embedded in Figure 2 are central determinants of welfare outcomes. When the agricultural supply curve is perfectly elastic, the price of the monotherapy does not fall. As the supply curve becomes less elastic, the reduction in the relative price of monotherapies increases. Government treatment policies affect the cross-price elasticity. Bans on monotherapy use and public-sector ACTs dampen the global response to a fall in the monotherapy price.

**Methodology**

To quantify the economic and public health impact of semi-synthetic artemisinin I integrate a microbiological-epidemiological model of malaria transmission and drug resistance adapted to account for the geographic spread of infection into a multi-market model depicting supply and demand for anti-malarials across 93 malaria-endemic countries. This specification allows
me to model the simultaneous interaction of several related markets over time. I determine the effects of introducing semi-synthetic artemisinin by contrasting two scenarios. In the baseline scenario ACTs and artemisinin monotherapies are procured from \textit{artemisia annua}, the agricultural input. In the second scenario a portion of ACTs is procured from semi-synthetic production technology; artemisinin monotherapies and the remainder of ACTs are plant-derived. Under both scenarios, consumption, disease prevalence and resistance patterns, and government treatment policies differ across countries.

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 \textit{artemisia annua} and drug manufacturers derive semi-synthetic artemisinin and an active “partner” ingredient. In the second stage of production, pharmaceutical companies transform the artemisinic acid into monotherapies or combine it with the partner ingredient to produce ACTs.

At any given time, a non-negative fraction of a country’s population is infected with malaria. Symptomatic individuals decide whether to seek treatment at public health facilities, purchase anti-malarials at the local drug shop, or forgo medication based on country-level treatment policies, the menu of drug prices and travel costs, and drug efficacy. Global
demand for each anti-malarial is the aggregation across symptomatic individuals in all countries who purchase the drug. Global market equilibrium occurs when the derived demand for *artemisia annua* is equal to the agricultural supply.

Consumption of a given drug in each country induces a spontaneous mutation in a fraction of the local parasite population, such that a small portion of parasites becomes resistant to the drug. Infection then spreads from one country to another through human and entomological migration. The new genetic characteristics of the parasite population dictate disease transmission and drug efficacy in the next period.

**Epidemiological Framework**

I modify the mathematical epidemiology model of malaria transmission and drug resistance set forth in Laxminarayan et al. (2010) to allow for the spread of infection across countries and to account for differences in the potency of artemisinin used in artemisinin monotherapies and ACTs. At any time $t$, the population in a country ($N$) is comprised of individuals who are susceptible to malaria infection ($S$), individuals who are currently infected ($I$), and individuals who have acquired temporary immunity ($M$). Treatment options available to infected individuals are the ACT (denoted by subscript $XY$) and the artemisinin monotherapy (subscript $X$). The infected population can be divided into four sub-groups: (1) those who are infected with a 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 only to the ACT partner ingredient ($I_y$), and (4) those who are infected with a strain that is resistant to artemisinin, the ACT partner ingredient, and (necessarily) the ACT ($I_{xy}$).

Figure 4 illustrates the temporal dynamics for each population group. Underlying equations of motion are reported in the Technical Appendix. From one period to the next susceptible individuals can remain susceptible, become infected by one of the four parasite

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6In this section and elsewhere, lower case subscripts \{x,y,xy\} refer to parasitic resistance to treatment, whereas subscripts \{X,XY\} refer to characteristics of the treatments themselves.
strains, or die of non-malaria related causes. Infected individuals can remain infected, return to the susceptible population as a result of successful treatment, develop immunity, or die of malaria or non-malaria related causes. In each period, a fraction of individuals \((a_i)\) receives treatment \(i\). The rate at which individuals receiving treatment \(i\) successfully recover and return to the susceptible population is denoted \(\rho_i^{TR}\). I assume that \(\rho_X^{TR} < \rho_{XY}^{TR}\) to reflect the fact that artemisinin derived for generic monotherapies is generally of lower potency than the artemisinin derived for ACTs. For a small fraction of infected individuals treatment causes mutation that induces resistance. These individuals move from one infected class to another. A portion of infected individuals who do not receive treatment or who receive treatment that is ineffective fight off their infection and move to the immune group. Infected individuals can also die of malaria or non-malaria-related causes. After certain number of
periods, individuals in the immune class lose their immunity and return to the susceptible population or die of non-malaria-related causes. Deaths are exactly offset by new births $B$, which enter the susceptible population.

**Geographic Spread.** After transmission has occurred, I allow infections to travel from one country to another via human and entomological migration. Infections flow from country $k$ to country $j$ at rate $\xi_{k,j}$. The total flow of infections for country $j$ in period $t$ is

$$
\sum_{k \neq j} \xi_{k,j} I^k_{i,t} - \sum_{k \neq j} \xi_{j,k} I^j_{i,t}
$$

where $I^j_{i,t}$ is the number of infected individuals in sub-group $i \epsilon \{w, x, y, xy\}$ in country $j$ at time $t$. Below I estimate $\xi_{j,k}$ for all pairs $j, k$ using a specification based on gravity estimation techniques from the international trade literature.

**Economic Framework.**

The fraction of infectious individuals treated with drug $i$ ($a_i$) is a central determinant of the epidemiological relationships described above. This variable is itself endogenous. In every period, symptomatic people choose whether to seek treatment and what form of treatment to seek based on the cost (and benefits) of all available options. If the global drug supply curve is upward sloping the price of treatment depends on the quantity demanded.

In this section I develop an economic framework to characterize the treatment decision and derive equations for the global demand and supply for anti-malarials. Outcomes are integrated with the epidemiological framework through the fraction of the infected population that receives treatment $i$ ($a_i$), the fraction of the infected population that carries a strain resistant to drug $i$ ($I_i$), and the rate at which individuals receiving treatment recover for drug $i$ ($\rho_i^{TR}$). I measure the economic and public health benefits of semi-synthetic artemisinin by comparing social welfare outcomes under the two scenarios described above.

**The Treatment Decision and Drug Demand.** Though *individuals* are infected and receive treatment, the treatment decision is made at the *household* level. This modeling
choice is reinforced by the high rate of infection and death among small children in sub-Saharan Africa who could not afford treatment on their own. When a household member experiences a symptomatic episode of malaria, the household pools its income and takes one of a finite set of possible actions. It can choose to seek treatment at the public health facility, purchase an anti-malarial at the local drug store, or forgo medication. The decision depends on a number of factors including the price and efficacy of available anti-malarials, the cost of travel to the clinic, and a number of household-specific characteristics.

I construct a multi-dimensional demand framework that relies on well-known horizontal and vertical differentiation models (Hotelling, 1990; Mussa and Rosen, 1978) to characterize the household decision. Households in extreme poverty that are limited in their ability to pay for effective treatment are likely to purchase a low quality drug or forego treatment. Moreover, households across all income categories may differ in their willingness to pay for treatment based on the bargaining power of the infected individual (or her primary caregiver). For example, a household may be willing to pay more for treatment if the infected person is the main source of income than if the infected is one of many small children (or vice versa). I represent this heterogeneity in households’ willingness and ability to pay for effective treatment by assigning each household an index, $\theta$, that takes values between zero and one. I assume that households are distributed uniformly between these extrema.

To characterize the simultaneous trade-offs between public and private health facilities I represent each country as a line with length 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. For simplicity I assume that the distributions of household address and willingness and ability to pay for treatment are independent.

Households first decide whether to attend the public health facility, purchase drugs at the local shop, or forgo formal treatment in favor of self-made remedies. Those that seek
treatment at the public health facility incur a per-unit travel cost, \( \lambda \), which is the sum of transportation costs and the value of lost time. Households that purchase an anti-malarial at the local drug shop do not incur a travel cost. Households who are unable to purchase an anti-malarial or determine that treatment is not cost-effective forgo treatment. A household located at address \( d \) receives indirect utility

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

from consuming one course of treatment \( i \in \{XY, X, Self\} \), where \( K \) is the perceived efficacy of the chosen treatment and \( C \) is the cost of obtaining treatment.

The efficacy of the ACT is defined as the share of the infected human population that carries a strain of malaria that is susceptible to treatment \( XY \), i.e., \( K_{XY} = \frac{I - I_{xy}}{I} \). The efficacy of the monotherapy is the relative recovery rate multiplied by the share of the infected population that carries a strain susceptible to treatment \( X \),

\[
K_X = \frac{\rho_X^{TR}}{\rho_{XY}^{TR}} \frac{I_w + I_y}{I}.
\]

The cost of obtaining treatment, \( C \), depends on government treatment policy. If ACTs are provided for free at public health clinics, treatment costs are as follows.

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

If ACTs are not subsidized, households that seek treatment at the public health clinic incur the travel cost plus the cost of the drug.

The box of height and length one in Figure 5 depicts the symptomatic fraction of a country’s population in \( (d, \theta) \) 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 under different policy scenarios.

Consider first a country in which anti-malarials are unregulated and unsubsidized. Let $\theta_{XY}$ denote the preference parameter for households indifferent between receiving the ACT at price $P_{XY}$ or receiving the monotherapy at price $P_X$. Assuming momentarily that households were only allowed to purchase at the local drug shop, households with preference parameter above $\theta_{XY}$ would purchase the ACT. Households with preference parameter above $\theta_X$, but below $\theta_{XY}$, would purchase the monotherapy. Households with a preference parameter below $\theta_X$ would go without treatment. Total demand for ACTs would be area $a+b$. Total demand for the monotherapy would be $c+e+f+g+h+i+j$. Households in area $k+l+m+n$ go untreated.
Now consider a country in which anti-malarials are not subsidized, and monotherapies are prohibited. Households with a preference parameter lying immediately below $\theta_{XY}$ face the trade-off between purchasing the ACT or foregoing treatment in this policy environment. Because these households value effective treatment relatively highly, many of them will choose now to purchase the ACT. Households with preference parameter lying immediately above $\theta_X$ do not value highly (or are unable to pay as much for) effective treatment. These households now choose to forego treatment. As a result, the preference parameter for the consumer in different between purchasing the ACT or foregoing treatment, $\tilde{\theta}_{XY}$, lies between $\theta_{XY}$ and $\theta_X$. In this policy environment, total demand for ACTs is area $a+b+c+e+f$. Households in area $g+h+i+j+k+l+m+n$ do not receive treatment.

When ACTs are subsidized at the public health clinic, households face a multi-dimensional decision. They first decide what anti-malarial they would purchase given only the choice to purchase at the local drug shop. They then decide if they would be made better off by traveling to the clinic. The vertical segment running from point $(d_1, \theta_{XY})$ to point $(d_1, 1)$ describes the location of all households who are indifferent between purchasing the ACT at the local drug shop or traveling to the clinic. Denote this segment $d_{XY}$.

The segment running from point $(d_1, \theta_{XY})$ to point $(d_2, \theta_X)$ describes the location of households who are indifferent between purchasing the monotherapy at the local drug shop or traveling to the clinic. Denote this line $d_X$. The segment below $d_X$, running from $(d_2, \theta_X)$ to $(1, 0)$, describes the location of households who are indifferent between receiving no treatment or traveling to the public health clinic. Denote this segment $d_{Self}$. The slopes of $d_X$ and $d_{Self}$ are finite and the slope decreases as one moves from $d_X$ to $d_{Self}$ because households in this portion of the box would receive a more effective treatment at the clinic than they would at the drug shop. At the same time, as one moves downward along $\theta$, the subjective valuation of this trade-off diminishes. The household with preference parameter $\theta = 0$ is indifferent between traveling a distance of $\epsilon$ to receive a free ACT at the clinic or foregoing treatment because the willingness and ability to pay for treatment is zero. Define
as the concatenation of segments \(d_{XY}, d_X, \) and \(d_{Self}\). Households lying to the right of \(Z\) in area \(b+f+j+n\) attend the clinic. Households to the left purchase at the local drug shop. Total demand for the ACT is \(a+b+f+j+n\). Demand for the monotherapy is \(c+e+g+h+i\).

Households in area \(k+l+m\) go without treatment.

Lastly, consider a policy environment in which ACTs are subsidized at the public health clinic and monotherapies are prohibited. Combining the results from the monotherapy prohibition and the “public-sector ACT subsidy” policy environments, households with preference parameter \(\tilde{\theta}_{XY}\) are indifferent between purchasing the ACT at the local shop or receiving no treatment. Households at location \(d_1\) with preference parameter between \(\tilde{\theta}_{XY}\) and 1 are indifferent between purchasing the ACT at the shop or traveling to the clinic. The segment on which households are indifferent between receiving no treatment and traveling to the clinic lies between points \((d_1, \tilde{\theta}_{XY})\) and \((1, 0)\). Total demand for the ACT is \(a+b+c+e+f+i+j+n\). Households in area \(g+h+k+l+m\) go without treatment.

Treatment outcomes for the four policy environments are summarized in Table 2. Note that 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 \(\theta\) parameter choose not to travel to the clinic. Two types of corner solutions 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 clinic visits change in this situation. For example, if the price of the monotherapy is sufficiently high and its efficacy is sufficiently low, the household indifferent between purchasing the monotherapy and foregoing treatment will have a higher preference parameter than the household indifferent between purchasing the ACT and the monotherapy. In these circumstances, the artemisinin monotherapy is not purchased at the local drug shop. If this situation occurs in a setting in which ACTs are subsidized in the public sector, \(Z\) becomes discontinuous between segments \(d_{XY}\) and \(d_{Self}\). Alternatively, suppose travel costs are sufficiently low that for some preference parameter, all households lying above that preference parameter choose to travel to the public clinic. In
this case $\mathcal{Z}$ becomes kinked and vertical at the y-intercept. Analytical solutions under these scenarios are reported in the Technical Appendix.

**Supply.** Global production of anti-malarials occurs in two stages. First, farmers grow *artemisia annua*, and pharmaceutical companies manufacture the partner ingredient. The marginal cost of producing *artemisia annua*, $w_A = a + b(Q_X + Q_{XY})$. I assume the manufacture of the partner ingredient is a synthetic process, and even in the short run firms have excess capacity and can increase or decrease production at constant marginal cost, $w_Y$.

Generic manufacturers transform artemisinin into monotherapies. Pharmaceutical companies combine artemisinin and the partner ingredient into ACTs. These activities occur using fixed proportion technologies. The marginal cost of producing the monotherapy and the ACT is $MC_i = w_i + c_i$, where $c_i$ is a constant, product-specific transformation cost, which includes the cost of all additional inputs.

In the first scenario all artemisinin monotherapies and ACTs are produced using *artemisia annua*. The price of inputs is $w_A$ for artemisinin monotherapies and $w_A + w_Y$ for the ACT. In the second scenario, a portion $\psi$, of ACTs is produced using the semi-synthetic technology at constant marginal cost $w_S$. The remainder of ACTs are derived from *artemisia annua*. In this scenario, the agricultural supply curve is described by the equation $w_A = a + b(Q_X + (1 - \psi)Q_{XY})$. Drugs sold at local drug shops are priced at marginal cost.

**Market Equilibrium.** Global demand for anti-malarials is the sum of demand in each country. I solve for global market equilibrium by setting global demand equal to global supply and equating derived demand for *artemisia annua* with agricultural supply. In the second scenario, ACT producers are indifferent between deriving artemisinin traditionally or semi-synthetically. The market clearing cost of producing *artemisia annua* is equal to the marginal cost of procuring 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 eco-
nomic growth, resulting from sickness and death. (Gallup and Sachs, 2001; Laxminarayan et al., 2010; Lubell et al., 2014). Because the anti-malarial market exists to offset some of these costs, I include traditional measures of consumer and producer surplus in the welfare calculation. Consumer surplus serves as an aggregate measure of the short-run impact price changes have on household welfare by freeing up money (and/or time) formerly used to purchase treatment. Producer surplus captures the broader economic impacts of semi-synthetic artemisinin beyond disease transmission, drug resistance, and donor financing. The technology will negatively affect farmers of *artemisia annua* by reducing demand for plant-derived artemisinin.\(^7\) Social welfare is quantified as the present value sum of consumer surplus, producer surplus, donor and taxpayer outlays, and economic losses associated with mortality and morbidity over the period of analysis. A mathematical expression of the social welfare calculation is included in the Technical Appendix.

## Parameter Calibration

I simulate the model set forth above for 93 malaria-endemic countries on a time step of 10 observations per year over a period of 15 years.\(^8\) I choose this relatively short time horizon because 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. With the exception of the $\xi$, which represents the spread of infections across countries, and $\rho_x^{TR}$, the rate at which individuals receiving the monotherapy successfully recover and return to the susceptible population, all epidemiological variables are calibrated using values from Laxminarayan et al. (2010). These values are reported in Table A1 in the Technical Appendix.

I assume that only half of the artemisinin derived for use in monotherapies is of sufficient

\(^7\)Note that because I have assumed all drugs are priced at marginal cost, surplus to drug manufacturers and pharmaceutical companies is zero in all scenarios.

\(^8\)I exclude French Guiana, Mayotte, and Democratic Republic of the Cogno from the analysis because measures of the gravity variables obtained from the Centre d’Etudes Prospects et d’Informations Internationales (“CEP-IT”) database used in the geographic spread analysis are unavailable for those countries.
potency to successfully treat malaria, i.e., $\rho_{TR}^X = 0.5\rho_{TR}^{XY}$. This assumption reflects the reality that monotherapies range in formulation from generic medications to herbal teas. Derivation processes used in the production of these products are commonly “low-tech” and produce a less potent form of artemisinin than that used in ACTs. The recovery rate for ACTs is defined as in Laxminarayan et al. (2010).

I account for differences in the rate of transmission across countries by grouping countries into three bins. Countries are characterized as either “low”, “medium”, or “high” transmission areas. “Low” transmission areas are assigned a mosquito density ($m$) of 0.25. The mosquito densities in “medium” and “high” transmission areas are 0.5 and 0.7, respectively. Consistent with Laxminarayan et al. (2010) I use no-drug, steady-state population shares to classify initial population sub-groups. Figure 6 reports initial population sub-groups as a function of the mosquito density in any given country. The vertical dotted lines in panel (a) correspond
Table 3: Transmission Scenario and Treatment Policy Calibration

<table>
<thead>
<tr>
<th>Transmission</th>
<th>Unregulated</th>
<th>Monotherapy Ban</th>
<th>Public-Sector ACT Subsidy</th>
<th>Mono Ban and ACT Subsidy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>13</td>
<td>30</td>
</tr>
<tr>
<td>Medium</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>27</td>
<td>32</td>
</tr>
<tr>
<td>High</td>
<td>0</td>
<td>9</td>
<td>4</td>
<td>18</td>
<td>31</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>7</strong></td>
<td><strong>17</strong></td>
<td><strong>11</strong></td>
<td><strong>58</strong></td>
<td><strong>93</strong></td>
</tr>
</tbody>
</table>

Drug consumption in each country occurs under one of four policy environments: (1) unregulated, (2) bans on monotherapy usage, (3) public-sector ACT subsidies, and (4) bans on monotherapy usage and public-sector subsidies for ACTs. Information on current governmental treatment policies in each country are taken from annual WHO World Malaria Reports. Table 3 disaggregates the country calibration by transmission scenario and treatment policy. Only 7 countries allow unregulated consumption of anti-malarials, each of which are low transmission areas. The vast majority of countries have adopted both public-sector ACT subsidies and monotherapy bans in conformance with WHO recommendations.

**Economic Calibration.** Figure 7 depicts the global demand for anti-malarials under the treatment policy and transmission calibrations summarized in Table 3. In each panel the price and efficacy of the other treatment are fixed at initial levels. As shown in Figure 7(a), global demand for ACTs is kinked and perfectly inelastic at high price levels. This shape reflects the fact that there exists a reservation price at which no consumer would purchase the ACT at the local drug shop. ACT demand is positive for prices at and above the reservation price because individuals who travel to the clinic continue to receive the ACT. At all points above the reservation price, ACT demand is perfectly inelastic because individuals who attend the clinic receive the ACT for free.

Figure 7(b) shows the success of monotherapy bans in reducing the global consumption of monotherapies. Even when \( P_X = 0 \), slightly less than 7 percent of the global symptomatic population receive the monotherapy. This representation is somewhat optimistic in that it assumes perfect compliance with prohibitions on monotherapies. As discussed above, the
informal private sector can be difficult to regulate, and the imposition of a monotherapy ban may not completely eliminate monotherapy consumption. Thus, global demand for monotherapies may be larger than is characterized in Figure 7(b).

Figure 7(c) depicts the relationship between travel costs and the treatment decision. 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, on average, are roughly equivalent in magnitude to the price of treatment itself. I calibrate the per-unit cost of travel as $\lambda = 3.75$. In the first-period equilibrium this cost is equivalent to the price of ACT treatment for households at location 0.27. 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.,

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9I leave for future research the development of a specification that incorporates the existence of “black markets” for anti-malarials.

The Technical Appendix includes detailed information on the calibration of economic variables. I assume the supply curve for *artemisia annua* is unit elastic in the baseline scenario to reflect the fact that production of *artemisia annua* is geographically constrained. I model the cost of producing ACTs semi-synthetically as a 10 percent reduction from the initial equilibrium ACT price. This assumption is in line with early estimates by the Global Fund (Fund, 2010). 10

**Geographic Spread.** I use a specification based on gravity estimation from the international trade literature to estimate the rate at which infections spread between countries. My logic is as follows. The number of infections in a country at any given time is a function of country-specific conditions, including past infections and the country’s current ability to monitor and prevent disease transmission, and the inflow of infections from all other countries. The rate at which infections flow from one country to another depends on the number of infections in the “exporting” country and the bilateral linkedness—or level of interaction—between the two countries. I use annual data from 2000 to 2014 to estimate this relationship for the 93 countries included in the simulations according to the following equation

\[ I_j^t = \alpha + \beta_1 X_j^t + \beta_2 \Gamma_{j,k}^t I_k^t + \Phi(t) + e_{j,k}^t \]  

(1)

where \( I_j^t \) and \( I_k^t \) are the number of infections in countries \( j \) and \( k \) at time \( t \), \( X_j^t \) is a vector of characteristics specific to country \( j \), and \( \Gamma_{j,k}^t \) is a vector of several common proxies for bilateral linkedness used in the international trade literature. I approximate \( \Phi(t) \) by including year-fixed-effects and a time trend in the regression. Estimated parameters \( \alpha, \beta_1 \) and \( \beta_2 \) measure the responsiveness of infections in country \( j \) to changes in \( X_j^t \) and \( \Gamma_{j,k}^t I_k^t \). The pairwise residual, \( e_{j,k}^t \), measures the change in infections at time \( t \) that is unexplained by changes in other observed variables.

10The assumption that semi-synthetic technology lowers the cost of production is also consistent with input price data. Prior to the widespread rollout of semi-synthetic artemisinin in January 2014, the average unit price of artemisinin imported into India was $475.59/kg. Since then, the price has dropped to $224.65.
Annual observations of the number of infections presumed and confirmed in each country are obtained from the WHO Global Health Observatory. Observations on distances, contiguity, language, and colonial history are obtained from the CEPII database (Mayer and Zignago, 2011). Population and GDP per capita are obtained from the World Bank. Summary statistics and estimation results are included in Tables A2 and A3 of the Technical Appendix. I calibrate the rate at which infections flow from country $k$ to country $j$ in the epidemiological-economic model as the estimated value of $\beta_2$ multiplied by the time-invariant proxies for bilateral linkedness:

$$\xi_{k,j} = \hat{\beta}_2 \Gamma_{j,k}$$

Figure 8 depicts the kernel density estimate of the calibrated values of $\xi_{k,j}$. I strongly reject the hypothesis that parameters in vector $\beta_2$ are jointly zero according to standard, post-estimation Wald tests. However, the “geographic spread” effect appears to be small. For most country pairs $\xi_{k,j}$ is, or is close to, zero and is negative in many cases. These findings are not surprising because my estimation of equation (1) is not strictly “identified”. My model does not distinguish between infections flowing in from country $j$ to country $k$ and out from country $k$ to country $j$. Thus, parameter $\xi_{k,j}$ is best interpreted as a net effect.
### Table 4: Average Annual Cost of Malaria, Million US$ (Present Value)

<table>
<thead>
<tr>
<th>Welfare Measure</th>
<th>Production Scenario</th>
<th>Impact of Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Plant-Grown</td>
<td>Semi-Synthetic</td>
</tr>
<tr>
<td>Consumer Surplus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACT (Clinic)</td>
<td>46.7</td>
<td>44.8</td>
</tr>
<tr>
<td>Total Local</td>
<td>10.3</td>
<td>15.4</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>2.4</td>
<td>3.2</td>
</tr>
<tr>
<td>ACT</td>
<td>7.9</td>
<td>12.2</td>
</tr>
<tr>
<td>Producer Surplus</td>
<td>121.4</td>
<td>12.1</td>
</tr>
<tr>
<td>Donor Financing</td>
<td>-85.4</td>
<td>-72.6</td>
</tr>
<tr>
<td>Morb &amp; Mort</td>
<td>-6,330.6</td>
<td>-6,204</td>
</tr>
<tr>
<td>Total</td>
<td>-6,237.6</td>
<td>-6,204.6</td>
</tr>
</tbody>
</table>

### Results

Using the calibrations discussed above I simulate the model for the “traditional” scenario in which all artemisinin monotherapies and ACTs are produced using plant-grown artemisinin and the “semi-synthetic” scenario in which a portion of artemisinin for use in ACTs is produced semi-synthetically. All artemisinin monotherapies and the remaining portion of ACTs are derived from plant sources. Table 4 reports average, annual present-value welfare outcomes under both production scenarios. External costs associated with morbidity and mortality are significantly larger in magnitude than all other welfare measures. Estimates of the average, annual cost of malaria under both production scenarios are consistent with previous literature (Gallup and Sachs, 2001; Sachs and Malaney, 2002).

A comparison of the two scenarios shows that the positive transmission externality associated with increased access to treatment in the semi-synthetic scenario strongly outweighs the negative externality associated with increased drug resistance on the global scale. The introduction of semi-synthetic artemisinin decreases the costs of donor financing and mortality and morbidity by approximately 15% and 2%, respectively, for a combined savings of $139 million per year, or $2.1 billion over the 15 year time horizon. Consumer surplus associated with treatment at the local drug shop increases by 50% and consumer surplus associated with treatment at the clinic falls by 4% as symptomatic individuals substitute in
favor of cheaper treatments at the local drug shop. The “short-run” gain to households that receive treatment is $2.9 million per year, or a 5% increase in total consumer surplus. Some of these savings are offset by losses in surplus for farmers of artemisia annua. The net result is a 1.7% reduction in the number of global infections and a $495 million increase in global social welfare over the next 15 years.

Panel (a) of Figure 9 shows the share of ACTs produced using the agricultural input in the semi-synthetic scenario over time. The introduction of semi-synthetic artemisinin has a substantial impact on the agricultural input market. On average, semi-synthetic production limits the use of artemisia annua to less than 25% of ACT production over the time horizon. Panels (b) through (d) of Figure 9 depict drug consumption over time under each scenario. In both scenarios, monotherapy consumption shown in panel (c) decreases faster than ACT consumption in panel (b) because resistance develops faster in monotherapy form than in combination form. Comparing between scenarios, one sees that the price reduction
Table 5: Avg. Increase in Country-Level Welfare by Treatment Policy and Transmission Area (%)

<table>
<thead>
<tr>
<th>Transmission</th>
<th>Unregulated</th>
<th>Monotherapy Ban</th>
<th>Public-Sector ACT Subsidy</th>
<th>Mono Ban and ACT Subsidy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>13.31</td>
<td>0.89</td>
<td>1.22</td>
<td>0.22</td>
<td>3.55</td>
</tr>
<tr>
<td>Medium</td>
<td>-</td>
<td>0.58</td>
<td>4.75</td>
<td>0.22</td>
<td>0.67</td>
</tr>
<tr>
<td>High</td>
<td>-</td>
<td>0.33</td>
<td>1.77</td>
<td>0.20</td>
<td>0.44</td>
</tr>
<tr>
<td>Total</td>
<td>13.31</td>
<td>0.56</td>
<td>2.38</td>
<td>0.22</td>
<td>1.52</td>
</tr>
</tbody>
</table>

associated with semi-synthetic technology increases the consumption of both drugs. The mean percentage of symptomatic infections that do not receive treatment across all periods (panel d) falls from 55.7% to 52.0% between the traditional scenario and the semi-synthetic scenario. Compared to the traditional, all-plant-grown scenario, the relative increase in the mean consumption of the monotherapy across all periods (28.6%) is greater than for the ACT (7.2%). These results are consistent with the “Alchian-Allen” effect discussed in the context of the simple static model.

However, the adoption of monotherapy bans in a large number of countries has restricted the absolute level of monotherapy consumption. Aggregating across the time horizon, only 3.6% of global symptomatic infections receive the monotherapy in the semi-synthetic scenario compared to the 44.5% of symptomatic infections that receive the ACT. Moreover, unregulated consumption of monotherapies occurs exclusively in “low transmission” areas, where resistance develops slowly.

Table 5 reports the percentage increase in country-level welfare resulting from the introduction of semi-synthetic artemisinin by treatment policy and transmission scenario as a simple average across countries in each category. The average impact of semi-synthetic artemisinin across all policy environments and transmission scenarios is a 1.52% increase in welfare over the 15 year horizon. Benefits are greatest in low transmission areas that do not prohibit the use of monotherapies or offer subsidized ACTs in the public sector. The impact is lowest in high transmission areas where ACTs are subsidized and monotherapies are banned. These results highlight the trade-offs between the externalities associated with
disease transmission and drug resistance.

In regions that do not subsidize ACTs, drug access is low, and the externality benefit of a marginal increase in drug consumption is large. In this context, the benefit of the absolute price effect results from the introduction of semi-synthetic artemisinin is largest. Moreover, the resistance externality is small in low transmission areas. In contrast, in areas that subsidize ACTs, drug coverage is high even before the introduction of semi-synthetic artemisinin. The external benefit associated with transmission is relatively small. If a country prohibits monotherapy use in addition to subsidizing ACTs, consumers do not experience the full effect of semi-synthetic technology on absolute price levels. Benefits at the individual-country-level are reported in Table A5 in the Technical Appendix as an annual, average per-capita gain in US dollars and as a percentage increase relative to the traditional, plant-grown-only scenario welfare outcome.

**Alternative Specifications and Sensitivity Analysis**

To test the sensitivity of results to my calibration assumptions I re-run the model using price elasticities of 0.4 and infinity for the *artemisia annua* supply curve. Table 6 reports global welfare outcomes under these alternative elasticity assumptions. When the agricultural input supply curve is perfectly elastic, monotherapy prices remain constant and are unaffected by the introduction of semi-synthetic artemisinin. The technology reduces the ACT price, in both absolute and relative terms. Compared to outcomes in the “baseline” scenario in which I assume a unit-elastic supply curve, semi-synthetic artemisinin induces a smaller increase in drug coverage, which leads to a smaller increase in the positive externality associated with disease transmission. However, the relative price effect generates a smaller negative externality associated with antimicrobial resistance, and drugs remain effective for longer.

A comparison of traditional-scenario and semi-synthetic-scenario outcomes under the infinite elasticity assumption in Table 6 shows that the introduction of semi-synthetic artemisinin leads to a present-value gain of $143.6 million per year, or $2.1 billion over the 15 year horizon,
Table 6: Welfare Outcomes Under Alternative Elasticity Assumptions

<table>
<thead>
<tr>
<th>Welfare Measure</th>
<th>$\epsilon = \infty$</th>
<th>$\epsilon = 0.4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consumer Surplus</td>
<td>Traditional Production</td>
<td>Semi-Synthetic Production</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>2.3</td>
<td>1.4</td>
</tr>
<tr>
<td>ACT (Local)</td>
<td>6.8</td>
<td>12.4</td>
</tr>
<tr>
<td>ACT (Clinic)</td>
<td>46.2</td>
<td>44.8</td>
</tr>
<tr>
<td>CS Total</td>
<td>55.3</td>
<td>58.6</td>
</tr>
<tr>
<td>Producer Surplus</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Donor Financing</td>
<td>-86.8</td>
<td>-72.9</td>
</tr>
<tr>
<td>Morb &amp; Mort</td>
<td>-6,319.4</td>
<td>-6,193.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>-6,350.9</strong></td>
<td><strong>-6,207.3</strong></td>
</tr>
</tbody>
</table>

compared to a $495 million gain over the time horizon in the baseline specification. Under this specification, the technological change induces a smaller gain in early periods compared to the baseline model. When the agricultural supply curve is infinitely elastic, only the price of the ACT falls. The price of the monotherapy remains constant. Thus, the absolute price impact is smaller than in the baseline. However, the technology induces a decrease in the relative price of the ACT. Accordingly, drug efficacy is preserved to a greater extent than in the baseline. As shown in Table 6, initial drug coverage is lower than in the baseline model. The relative price change decreases surplus associated with the consumption of monotherapies by 38% through substitution at the local drug shop away from the monotherapy in favor of the ACT. Surplus associated with ACT consumption at the local drug shop increases by 83%. Lower drug coverage generates only $58.6 million in consumer surplus in the semi-synthetic scenario, compared to $59.9 million in the baseline scenario because the absolute price impact is smaller. However, the long-run effect is a 6% increase in consumer surplus from the traditional, all-plant-grown scenario to the semi-synthetic scenario compared to a 5% increase under the baseline because reduced monotherapy consumption preserves the efficacy of artemisinin in later periods. The $13.9 million annual reduction in donor financing costs and $126.4 million reduction in the economic losses related to mortality and morbidity are also larger in magnitude and as a percent change than the baseline outcomes. Moreover,
the perfect elasticity assumption implies no scarcity rents for producers of *artemisia annua*, and thus, no losses in producer surplus to offset gains related to malaria.

Table 6 reports results for an agricultural supply curve with an elasticity of 0.4. For a less elastic agricultural supply curve, the introduction of semi-synthetic artemisinin induces a greater reduction in the relative price of the monotherapy as a result of the semi-synthetic technology. This relative price effect increases the negative externality associated with drug resistance. The impact of semi-synthetic artemisinin is positive, but the reduction in the disease burden is smaller than in the baseline or under the assumption of an infinitely elastic agricultural supply. Donor financing costs fall by only 7% compared to 15% and 16% under the previous supply assumptions. Economic losses associated with morbidity and mortality fall by only 1%. Despite lower drug prices, there is no difference in the impact on consumer surplus between the two scenarios.

I next test the sensitivity of results to the spatial externality associated with the geographic spread of infection by running the model without allowing malaria to travel between countries. Panels (a) and (b) of Figure 10 show the impact of introducing semi-synthetic artemisinin on infections per capita in the most and least infected countries as a percent change from outcomes in the traditional, all-plant-grown scenario over the time horizon. In both panels the solid line depicts the impact of the technology in the baseline scenario in which geographic spread occurs at rates $\xi_{k,j}$ as estimated in equation (1). The dash-dotted
line represents the impact of the technology when infections do not travel between countries. As shown in Figure 10, the geographic spread of infection (as calibrated) has a minimal impact on disease prevalence. When I re-run the baseline model without allowing infections to travel, the average percentage change in disease prevalence in the most infected country decreases in magnitude on the order of $1\times10^{-6}$. The impact of removing geographic spread is slightly larger in the least infected country, but still negligible. The average percentage change in disease prevalence in the least infected country decreases in magnitude on the order of $1\times10^{-3}$. The reduction in the total number of global infections as a result of the technology decreases by $1.56\times10^{-7}$.

Although my results appear to suggest that human and entomological migration are not a major source of infection in the context of malaria, these findings should be taken with extreme caution. As discussed above, my model does not distinguish between the inflow and outflow of infection, and, thus, parameter $\xi_{k,j}$ is best interpreted as a net relationship. If these inflows and outflows are roughly equivalent, one would expect this net relationship—as measured—to be small. I leave for further research the development of a more rigorous identification strategy to isolate the effects of international trade and migration on global malaria outcomes.

**Conclusion**

This research evaluates the economic impact of recent technological change in the market for anti-malarials. I show that the introduction of semi-synthetic artemisinin has two effects on the price of artemisinin-based anti-malarials. First, semi-synthetic artemisinin lowers the _absolute_ price of ACTs and artemisinin monotherapies. Second, semi-synthetic artemisinin lowers the _relative_ price of artemisinin monotherapies. These price impacts have contrasting impacts on the two externalities associated with treatment of infectious disease. The reduction in _absolute_ price levels increases drug coverage and the positive externality associated with reductions in disease transmission. The _relative_ price change increases the negative ex-
ternality associated with drug resistance. In any given country the size of these externalities depends on a number of factors, including the current level of drug coverage, the prevalence of disease, and the rate at which infections flow into and out of the country.

To quantify the effect of semi-synthetic artemisinin on global welfare, I integrate a microbiological-epidemiological model of malaria transmission and drug resistance into a partial equilibrium model depicting the supply and demand for anti-malarials across 93 endemic countries. I account for differences across countries in anti-malarial consumption, disease prevalence and resistance patterns, government treatment policies, and the geographic spread of infection. I find that the net externality generated by the technological change is overwhelmingly positive and more than offsets losses to farmers of the agricultural input.

Global savings in donor costs and malaria-related mortality and morbidity range between $63–$140 million per year. Comparing these outcomes with the latest malaria incidence and finance estimates from the WHO provides a sense of scale for these results. The annual savings induced by semi-synthetic artemisinin equate to approximately $0.50 per case or $200 per death in 2014 and represent about a quarter of annual ACT spending by the international community. The $945 million to $2.1 billion savings over the 15 year time horizon constitute a substantial portion of the total $2.5 billion outlay in global financing across all malaria control programs in 2014.

Country-level outcomes highlight the complex trade-offs policymakers face in managing the multiple externalities associated with malaria. Countries that have instituted monotherapy bans receive the smallest benefits of semi-synthetic artemisinin. Prohibitions on the use of monotherapies slow the rate of drug resistance but also makes aggregate demand for anti-malarials less price elastic. As a result, the price reduction from the new technology induces only a small change in drug coverage. Accordingly, the benefits of the technological change are small in those countries because the positive externality associated with receiving treatment outsizes the negative externality associated with drug resistance. Drug demand is also relatively unresponsive to market prices in countries that have implemented public-sector
subsidies for ACTs. However, the reduction in ACT prices generates large savings for taxpayers and international donors. The largest benefits accrue in countries where anti-malarial treatment remains unregulated.

Overall, my findings highlight the importance of public-private partnerships focused on product development as a driver of innovation in the context of malaria and infectious disease more broadly. The development of technologies like semi-synthetic artemisinin may not be profitable for private companies. By resolving incentive-based and financial barriers to research, these collaborations work to reduce the global burden of disease by managing global externalities related to disease transmission and antimicrobial resistance.

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