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Nets or Vaccines: Malaria Vaccine Research

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Introduction

Malaria is one of the most prevalent and debilitating diseases in the world. In 2010 the World Health Organization (WHO) reported there were 219 million clinical cases of malaria resulting in 660,000 deaths, most of which occurred in Africa. (CDC, 2012c) This parasite has been targeted by the WHO for eradication (Tanner & Savigny, 2008) after decades of focus on management and treatment due to spreading strains of drug-resistant malaria. (Turschner & Efferth, 2009, p. 206) This new battle focuses on preventing malaria infection through educational programs, mosquito nets and insecticide. In addition to these efforts, research is being conducted into the creation of a malaria vaccine. However the development of this vaccine has proven enormously costly and despite a successful trial (Times, 2013) it still remains to be seen if the current development will be more effective than the tried and tested methods.

This paper will begin with a description of malaria and the unique challenges facing researchers as well as an examination of the impacts of malaria on Africa. It will then investigate the impact that the current eradication efforts have had on the disease and provide historical context for malaria eradication. The malaria vaccine will then be examined, both in terms of the successful trial of the RTS,S vaccine and the ongoing development of other vaccines. It will show that while the current vaccine has promise, the high cost relative to other methods of

infection prevention will limit the utility of the vaccine and suggest that a malaria vaccine would at best provide an incremental benefit to existing treatments rather than a new treatment option.

Malaria

Malaria is caused by a mosquito-borne parasite of the genus *Plasmodium* found in tropical climates. Five varieties are known to exist, of which *Plasmodium Falciparum* is the most widespread and deadly. (CDC, 2012c) This is not to say that it is uniquely lethal, as *P. Vivax* has been shown to be equally dangerous (Baird, 2007, p. 533) though it is not as widespread as *Falciparum*. (Baird, 2007, p. 534) That said since *Falciparum* is responsible for the majority of deaths, it is the strain that has been the focus of vaccine research. (Sanaria, 2013) The parasite infects its host through mosquito saliva during feeding. It then travels to the liver to reproduce into its infectious form, after which it moves into the blood stream, destroying red blood cells as part of its reproductive process. (CDC, 2012a) If left untreated it will cause jaundice, kidney failure, coma and eventually death. (CDC, 2012c)

Developing an effective treatment or vaccine has proven difficult due to the adaptability of the parasite. (Turschner & Efferth, 2009, p. 206) The various species of *Plasmodium* show high genetic variance due to a rapid lifecycle and as a consequence human treatment efforts have created drug resistant strains. Research has also been complicated by the numerous life stages of the parasite, each of which requires a different method to attack. This has consequently raised the cost of research and spread the research focus. It has proven to be vicious cycle of increased research leading to increased treatment leading to the need for more research. The parasite is proving to be so capable of adapting to treatment that previously promising research is now increasingly useless. (CDC, 2010)

Malaria is of particular concern not just for the substantial human cost but also for the economic costs. As previously mentioned, the WHO recorded 660,000 deaths in 2010, but estimated that the total could have been as high as 836,000 due to underreporting and misdiagnosis. (WHO, 2013a) Other sources indicate that the WHO estimates are still too low, with some claiming a million deaths per year from malaria. (Sanaria, 2013) In addition, studies have shown that the presence of malaria cripples economic growth and development. A study by the Institute for the Study of Labor indicated that the presence of malaria reduces income by half. Previous research had shown that countries with high incidence of malaria had a GDP per capita of $1,526 compared to $8,268 in non-malaria burdened countries. The study claimed that malaria infection accounted for approximately $3,371 of that lost productivity. (Gollin & Zimmermann, 2007, p. 20) Prior research has shown that malaria saps the productivity and financial savings of nations through medical care and sick leave, ensuring that poverty remains rampant despite economic growth. (Sachs & Malaney, 2002, p. 684) Thus the treatment and elimination of malaria provides benefits not only in terms of longevity but quality of life.

Eradication

Efforts to eliminate malaria from global hotspots, particularly sub-Saharan Africa, dropped off during the 1970's and the focus switched to treatment. This decision came on the heels of successful elimination of the parasite in the United States, Caribbean and Europe. The change in focus has been attributed to the failure of such programs in Africa. (Tanner & Savigny, 2008) The methods used in previous efforts simply did not appear to be as effective in Africa and so interest waned. In the United States, the precursor to the modern Centers for Disease Control and Prevention, the Office of National Defense Malaria Control Activities led the effort in what became known as the National Malaria Eradication Program. This program was heavily

dependent on the insecticide DDT, which in addition to being sprayed over breeding sites was applied to homes in infected areas. The agency also employed screens for doors and windows and the drainage of breeding sites to eliminate the disease. (CDC, 2012b) The goal was to prevent new infections and eliminate mosquito breeding sites. The effort proved effective. By 1951 the disease was considered eradicated in the US and no further wild cases are reported. All current malarial infections of US citizens originate outside US borders. This strategy also worked in the Caribbean and Europe. Without a transmission vector, the parasite died out.

This approach was not successful in Africa, though the exact reason is uncertain. Elimination was being phased out while DDT was still in use so that is not the critical factor, though the lack of health services available is a frequently cited culprit. Regardless, modern eradication programs tend not to focus on the use of insecticide. Instead the programs focus on the use of mosquito nets and education programs to prevent bites and thus eliminate infections. The WHO recommends sleeping under insecticide treated nets (ITNs) as an effective means to prevent infection. (WHO, 2007, p. 1) Mosquitoes are opportunistic feeders and tend to be most active at night when victims cannot defend themselves and studies have shown that sleeping under a mosquito net can reduce probability of infection by 39% and using an ITN reduces rates by 50% for stable malaria and 43%-62% for unstable malaria. (Christian Lengeler, 2004) Thus the Non-Governmental Organizations (NGOs) involved in malaria eradication, of which Malaria No More is the most prominent, focus their efforts on providing long lasting insecticidal nets (LLINs) (Malaria No More, 2013) which are a newly developed form of ITN netting which is designed to maintain effectiveness for three years. (WHO, 2007)

In the case of Malaria No More (MNM), the nets are provided as part of a package of eradication measures including providing low cost medication and dedicated education programs

to civilians and diagnostic equipment to health services. The intention is to convince more Africans to sleep under the nets that MNM provides and to change their behavior so as to not get infected while improving care for those who are infected. MNM contends that education is the critical factor in preventing infection and death and that distribution and treatment only work when education is also present. They may have a point. WHO statistics show that since 2006, when MNM began operations, malaria deaths are down by 33% in Africa. (Malaria No More, 2013) However, one should be careful about the value of this statistic as MNM's direct impact is difficult to quantify. That said Tanzania and Senegal where MNM launched its combined education and distribution program saw tremendous declines in infection rates, though for reasons not known both stopped reporting to the WHO in 2009. During their reporting period Senegal experienced a 67.46% decrease in reported deaths and Tanzania saw a remarkable 95.99% decrease. Figure 1 provides the raw data on malaria deaths reported to the WHO by seven countries where MNM is active and three neighboring countries without an MNM presence (Rwanda, Ethiopia, and Sierra Leone). Figure 2 breaks the data down graphically by the type of aid MNM provided.

Figure 1

Malaria Deaths Reported to the WHO (WHO, 2013b)

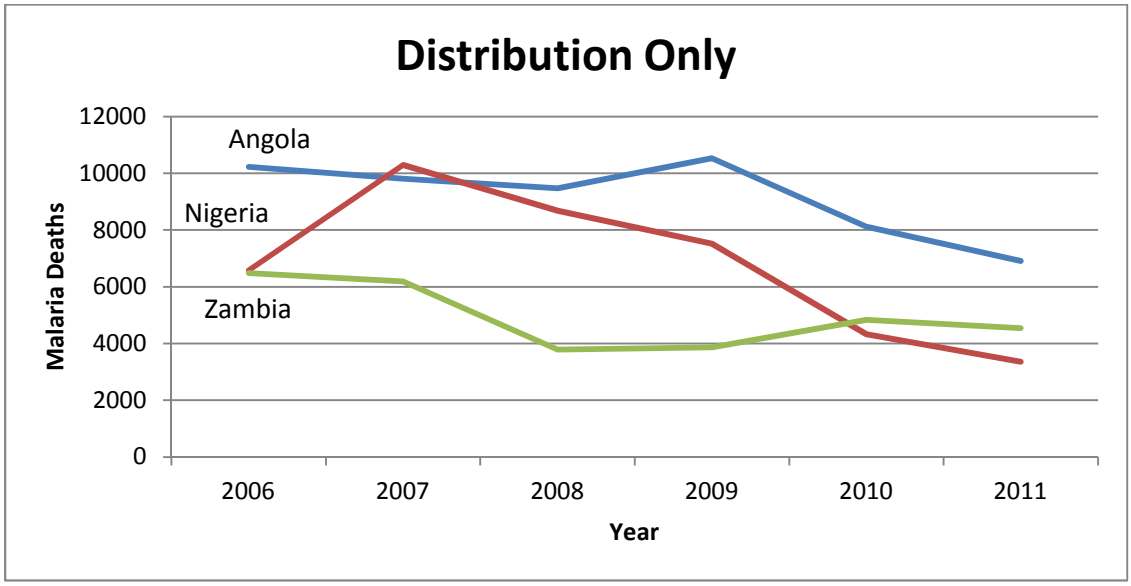
	Sierra Leone	Ethiopia	Rwanda	Senegal	Tanzania
2006	90	1357	2486	1678	20962
2007	324	991	1772	1935	12593
2008	871	1169	566	741	12434
2009	1734	1121	809	574	840
2010	8188	1581	670		
2011	3573	936	380		

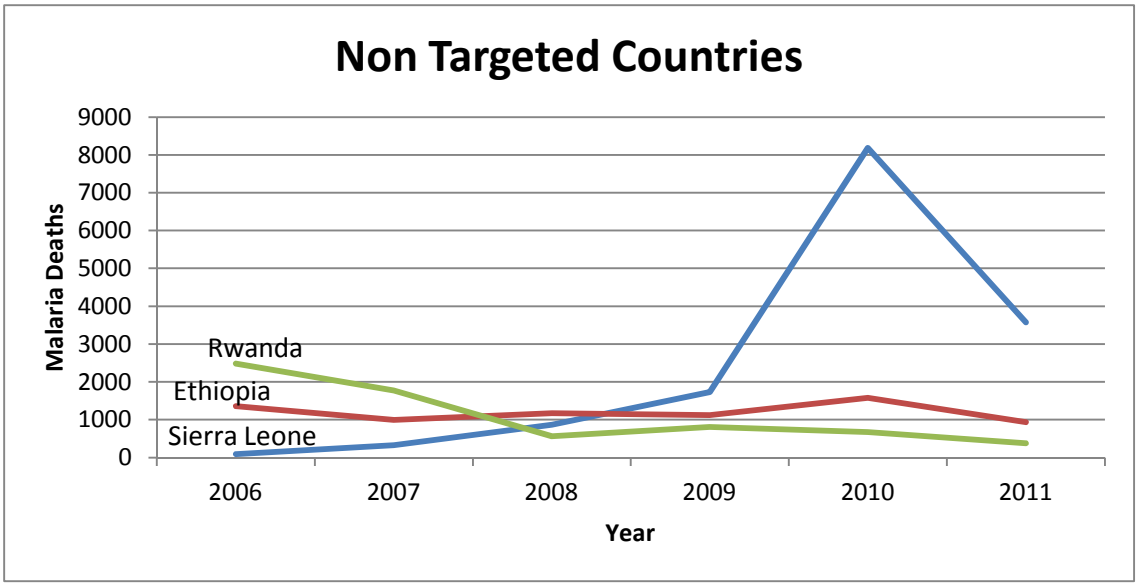
	Angola	Nigeria	Zambia	Cameroon	Chad	Kenya
2006	10220	6586	6484	930	837	40079
2007	9812	10289	6183	1811	617	
2008	9465	8677	3781	7673	1018	
2009	10530	7522	3862	4943	221	
2010	8114	4328	4834	4536	886	26017
2011	6909	3353	4540	3808	1220	713

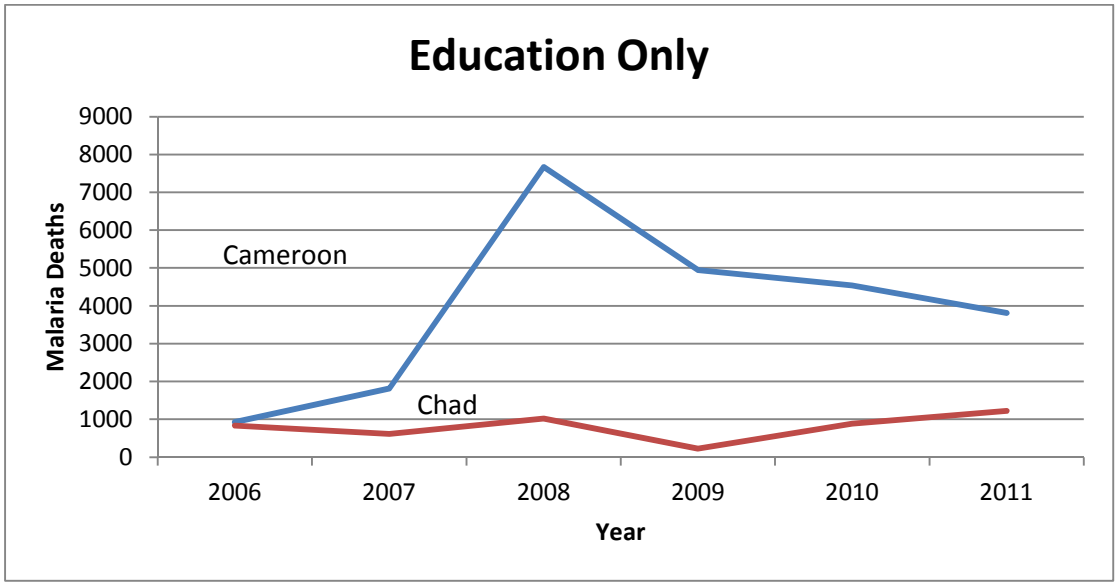
	Sierra Leone	Ethiopia	Rwanda	Senegal	Tanzania
% decrease 2006-2009	-1826.67	17.39	67.46	65.79	95.99

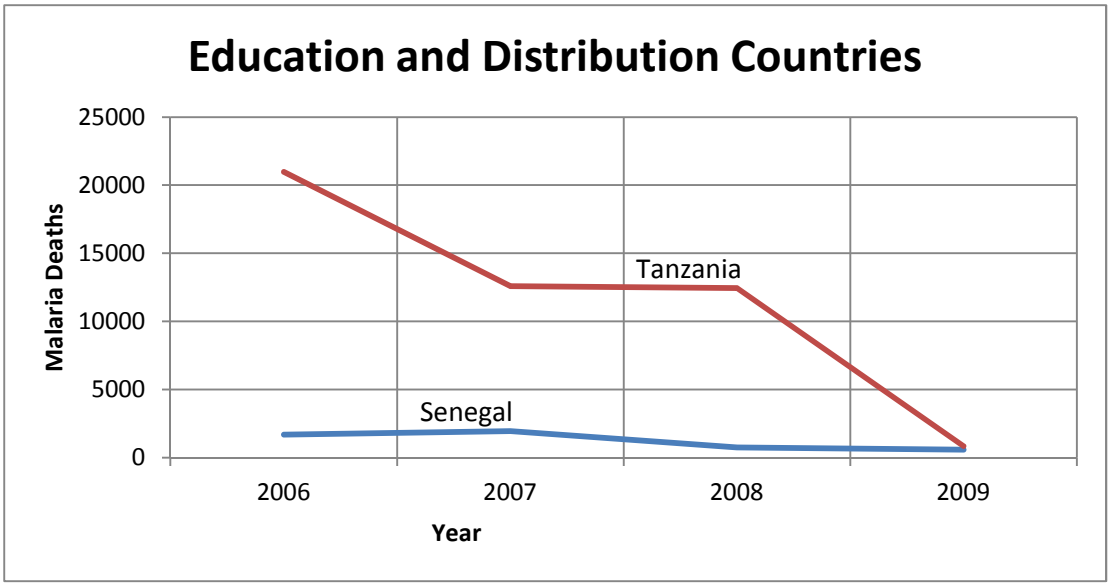
	Angola	Nigeria	Zambia	Cameroon	Chad
% decrease 2006-2009	-3.033	-14.21	40.44	-431.51	73.60

Figure 2




Non Targeted Countries
Malaria Deaths
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
Rwanda
Ethiopia
Sierra Leone
2006
2007
2008
2009
2010
2011
Year


Education Only
Malaria Deaths
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
Cameroon
Chad
2006
2007
2008
2009
2010
2011
Year



No explanation has been given by the WHO or government sources for the end of reporting by Senegal and Tanzania (Kenya's gap was due to political turmoil). These two countries were the only beneficiaries of MNM's combined program. Of the countries where MNM had only distribution or education programs only Zambia and Chad saw decreases during the period Senegal and Tanzania were reporting. Compared to the countries where MNM had no presence (Sierra Leone, Ethiopia and Rwanda) it does appear that a combined distribution and education program for eradication has a noticeable effect on improving survival.

There are no direct data on what the MNM programs cost. MNM takes pride in being the recipient of funds from large donors such as the Bill and Melinda Gates Foundation as well as private donors and does not publicly report outlays or which nets are actually being distributed. Since the ultimate goal of this paper is a comparison with the malaria vaccine, the focus shall be placed on the physical prevention measures provided, LLIN mosquito nets. These nets are typically given away in keeping with WHO directives and MNM goals, but still cost MNM to purchase. However, looking at the commercially available models of WHO approved LLINs

provides some indication of the cost. (WHO, 2012) Searching major online stores and wholesalers showed the lowest advertised retail price for bed netting was $38.99 while the highest retailed at $149.99. This price range will be compared to vaccine prices. The actual sales are likely done at wholesale prices, but the exact discount is unknown and therefore cannot be included.

Malaria Vaccine

A vaccine against malaria has been under development for decades. This has come at tremendous cost and up until recently there were not any positive results. Despite positive studies and strong research into creating immunity to infection, no vaccine has been successfully brought to market. (Sanaria, 2013) There are many research and pharmaceutical companies involved, from multinational corporations like GlaxoSmithKline to Sanaria Inc. which only performs research into the malaria vaccine. Sanaria's efforts are focused on developing a long-lasting whole-parasite vaccine that would cause an immediate immune response to parasite infection, but there is no indication of when that vaccine will move from research into reality.

GlaxoSmithKline on the other hand has a vaccine undergoing clinical trials known as RTS,S or mosquirix. Working on the same principle as Sanaria's research, the RTS,S vaccine began an initial trial in 2011 (Kelland & Hirschler, 2011), which was completed by 2013. (Times, 2013) The trial was carried out in seven countries where malaria-prevention programs were already in effect and 75% of the participants slept under an ITN. The end result was that the vaccine provided immunity for 18 months in 47% of children between ages 4-17 and 27% of infants. (Times, 2013) The study required participants to undergo three injections of RTS,S over twelve months. (Kelland & Hirschler, 2011) No information is currently available about effectiveness after 18 months.

Bringing RTS,S to this stage cost GlaxoSmithKline $350 million, and it has received an additional $200 million from the Gates Foundation for clinical trials and final preparation. (Times, 2013) Sanaria has received grants totaling $35 million for the current fiscal year. (Sanaria, 2013) Given the high costs associated with the creation of the vaccine, GlaxoSmithKline has been tightlipped about the final price of the vaccine, saying only that it would be priced as low as possible. This is indicated to be five percent over manufacturing cost. (Kelland & Hirschler, 2011) While it is therefore impossible to guess the final price to purchasers (who will likely provide it to patients well below cost or free) it may be possible to extrapolate based on the cost of other GlaxoSmithKline vaccines. The CDC buys from GlaxoSmithKline among other companies and keeps pricing schedules for all their vaccine purchases. On the low end, GlaxoSmithKline sells the CDC its adult flu vaccine for $5.89 per dose, which is available for private sector purchase for $9.50 per dose. On the high end the HPV vaccine's CDC price is $100.85 and the private cost is $128.75 per dose. (CDC, 2013) The CDC explains the price difference as a function of its research-grant program, allowing it to buy discounted drugs that it has helped fund. The private price reflects the actual cost and profit margin of the manufacturers. Thus it makes sense that GlaxoSmithKline would sell an organization like MNM the private-sector price. These price extremes will be used to evaluate the cost to benefit for the malaria vaccine.

Comparative Analysis

Looking at the costs and benefits of LLINs and the RTS,S vaccine should provide some insight into whether the hundreds of millions of dollars spent in its development have been worthwhile. Since the exact model of LLIN that is most commonly provided is not known nor has the final price of RTS,S been set by the manufacturer, the low and high commercial prices

for known nets and vaccines will be used. It is also important to note that the vaccine price will reflect the need to triple-dose patients to receive immunity as per the procedure of the clinical trial. Thus we will assume a per-net retail cost of $38.99 or $149.99 and a single immunity cost for a GlaxoSmithKline vaccine of $28.50 or $386.25. The vaccine pricing is a reflection of the previously mentioned GlaxoSmithKline pricing schedule and the three dose treatment used in the clinical trial.

	Net	Vaccine	Cost Difference %
High Price	149.99	386.25	-61.16
Low Price	38.99	28.5	36.81

On the low end the mosquito net was approximately 37% more expensive than the vaccine while on the high end it was 61% cheaper. Taking that into account, the question becomes whether the cost difference is justified by the effectiveness. Recall that the RTS,S trial reported that 75% of participants slept under ITNs which provide a baseline reduction in infection of 50%. .75*.50=.375 So assume that the trial began with a baseline success rate of 37.5%. The success rates reported by the trial were 47% for children and 27% in infants over the control group, which as commentators noted were well below the levels normally considered acceptable for vaccines. (Kelland & Hirschler, 2011) Taking those values into account, we can estimate the overall effectiveness of the vaccine as follows: .375*.47=.17625; .375*.27=.10125 Thus the vaccine may only have accounted for 10.1% to 17.6% of the total infection prevention in the trial.

Conclusion

Given that result, we can conclude that on the high end the vaccine's cost is not warranted, as it is not providing 61% more protection than a mosquito net. If GlaxoSmithKline is

able to keep costs down close to the low end then the cost could be justified as the cost savings of the vaccine vs. the net is positive. It is still higher than the benefit that the current vaccine provides, indicating some amount of inefficiency, but that may be forgivable if the vaccine is viewed as complementary to the rest of the eradication program. However, the question will still remain as to whether this justifies the current expenditure to arrive at the RTS,S vaccine. Given GlaxoSmithKline's outlays spent researching the drug it is hard to imagine that the price will be as low as flu vaccines, which would erode the benefit of the vaccine over the provision of nets. Those involved in malaria eradication will need to closely follow the ongoing development of RTS,S and other emerging vaccines to determine if the cost is justified. If the price remains high the vaccine will prove problematic for widespread distribution and would necessarily be viewed as a luxury rather than a necessity. The overall effectiveness and reliability of mosquito netting would necessarily take priority over the marginal benefit of the current vaccines. This issue is still evolving, so as more trials are conducted this analysis will become more informed and precise. Additional research is also necessary to determine the effect that eradication efforts are having on infection rates. As of this moment it does not appear that the benefit of research into the malaria vaccine has been worth the cost, and it would be better to focus on reducing infection using known means. Given the costs associated with treatment and the continued prevalence of malaria within Africa it may be time to shift focus back to eradication. In those countries where eradication worked malaria treatment is a non-factor and has freed up considerable manpower and funding for other health concerns, while as long as the parasite survives in Africa there will always be a risk that the disease could adapt to treatment methods and return to epidemic levels. Given the continued costs of treatment and development of new medications and vaccines it is worth consideration.

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