The Future of the U.S. Foreign Medical Policy: A Biological Understanding of Malaria in the U.S. President's Malaria Initiative

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Abstract

Malaria is a dangerous disease caused by the bite of an infected mosquito. Although some countries have managed to control and eliminate the disease, many still remain weighed down by the medical burden. In 2005, President W. Bush established the U.S. President's Malaria Initiative (PMI) with the intention of the United States providing aid to Sub-Saharan African Countries to eliminate malaria. PMI has remained an important part of US foreign policy, and one of the leading policies to combat malaria, receiving consistent bipartisan support. In order to properly combat malaria, a comprehensive strategy is needed, one that also considers and addresses the biology of the disease. The biological complexity of the disease calls for a thorough foreign policy that highlights technical approaches to control the disease. Effective policy requires an in-depth understanding of the biological mechanisms of the disease and targets the methods and treatments that keeps its spread controlled. This paper aims to analyze the biological mechanisms of malaria PMI addresses, to ultimately come to the conclusion that it effectively and comprehensively targets its biology to help lead the world to global malaria elimination.

Research question: Has the U.S. President's Malaria Initiative taken the biological components of the disease fully into account to properly combat the malaria epidemic? To what extent can this policy then be used as a foundation for future medical foreign aid policies?

I. Introduction

Malaria is a deadly disease that has continued to plague millions worldwide. This destructive health epidemic is caused by just the bite of the small, infected, *Anopheles* female mosquito. Malaria has been a leading public health crisis for decades. Some countries, including the United States, have successfully eradicated the disease, while many others are still struggling to control it. According to the 1850 U.S. Census, malaria used to be one of the leading causes of death where 45.7 out of every 1,000 deaths were caused by the disease (Hong, 2007). However, the United States established the National Malaria Eradication Program to aid 13 southeastern states with elimination efforts (Center for Disease Control and Prevention [CDC], 2018). Through targeted efforts with insecticide application to homes and buildings, combined with removal of mosquito breeding sites and improved drainage, this program was successful when the U.S. became malaria free in 1951 (CDC, 2018). This shows that malaria was a significant health issue in the United States, but it was able to recover and officially eliminate the disease, setting a precedent that it is realistic to go from a malaria-burdened country to one which has eliminated the disease.

The success of the US and other foreign countries has helped dictate foreign policies to try and help other countries on their path to elimination. One of the most important policies that was created in the United States' success was the U.S. President's Malaria Initiative (PMI), established in 2005 by Former President Bush. This was initially a 5-year $1.2 billion program that was supposed to provide aid to combat malaria in 15 sub-Saharan African countries ("About Us", n.d.). This policy has continued to grow and provide life-saving interventions and support countries still battling malaria. PMI now supports 27 sub-Saharan African countries and three programs in the Greater Mekong Subregion in Southeast Asia. Despite the staggering

polarization in the US government, PMI has continued to receive bipartisan support to become one of the leading international programs to help eliminate malaria.

Although caused by a tiny insect, malaria is highly complex and requires a targeted approach to its biological mechanisms to properly eliminate the illness. It requires differing strategies depending on the timeline, whether that be prevention or treatment. Although support purely through foreign aid can be beneficial, it is also critical for policies to also incorporate mechanisms that target the disease such as prevention and treatment options. One important part of PMI is the persistent research to ensure the data for current methods of prevention and treatment are up to date. This paper will examine the biological components of malaria and whether PMI properly targets these aspects.

Malaria is a complex disease that requires multiple mechanisms to be properly controlled. The use of well-established methods for prevention, control, and treatment are essential to address the disease from all angles. PMI consistently has proven that it is able to evolve to different environments and stay up to date with new research to ensure that it is providing the best care and information possible. PMI seems to understand the complexity of the disease and the challenges that the biology of the disease poses for proper and long-term control. It uses tools such as insecticide treated nets, indoor residual spraying, and artemisinin-based combination treatments to combat malaria. This initiative has proven itself to be a forward-thinking policy that strives to provide the best care, support, and information for millions of people while actually addressing the biological mechanisms of malaria.

Not only does PMI target key biological aspects of the disease to properly combat malaria, it also establishes institutions and a framework that sets its partner countries up for

success to handle malaria and other diseases better on their own. PMI understands it is critical to not just do the work for the affected countries but provide them with the tools and support they need to strengthen their own healthcare system. This has lasting positive effects that helps establish a strong and resilient system that is going to be vital as health crises continue to plague countries and the world. Foreign policies are key for providing support amongst different countries and become increasingly important when dealing with public health.

PMI has established a solid foundation for public health foreign aid. It combines the important parts of a foreign policy with the biology of the disease which is critical to properly address the issue. PMI has comprehensively examined the biological aspects of malaria to properly address the disease thoroughly. It not only dives deep into the science of the disease, it also recognizes its complexity and is adaptable to new research, resistant strains, and other biological issues they may encounter. Foreign aid for health-related issues is going to continue to be an important part of the United States' policy, as seen through the COVID-19 pandemic, which makes it increasingly important to analyze former and current policies to see what works and what doesn't. PMI has helped combat a major disease, one that's still being controlled and eradicated, and is a good policy to examine. Its lengthy existence allows for an analysis of its development and how it has adapted to changing research and new discoveries. In addition, PMI's rigorous research into the malaria disease along with its structured yet flexible approach offers a unique perspective into US foreign policy, and is an important one to use when designing future foreign medical policies.

Within this paper, I will address the biology of malaria to lay the background of the disease and the key components and mechanisms that need to be targeted. This will help provide background information to better understand the disease and why it is critical to target the

specific biology of malaria. I will then introduce the PMI policy and lay out the general basis for its creation. I will also go into the specifics of the key components of the policy, ones that are critical for addressing the biology of the disease. This includes insecticide treated nets (ITNs), indoor residual spraying (IRS), artemisinin-combined therapies (ACTs), and treating malaria during pregnancy and in childhood. I will then analyze whether PMI properly addresses the key biological components of malaria in order to effectively combat and eliminate the disease. I will finish the paper looking at the legacy of this policy and its impact on future medical foreign policy in the United States. I ultimately come to the conclusion that PMI sets a solid foundation for future foreign medical policies by comprehensively and effectively targeting the disease at its core biological level to properly lead countries to control or eradication.

II. The Biology of Malaria

In order to better understand the disease and thus the success of the policy, it is important to know the underlying biological mechanisms that make this disease so dangerous. Malaria infections in humans are caused by the bite of a specific infected mosquito, the female *Anopheles* mosquito (Crutcher & Hoffman, 1996). Within this species, there are currently only five strains that infect humans: *Plasmodium (P.) vivax, P. ovale, P. malariae, P. knowlesi,* and *P. falciparum* (“Fact sheet about malaria,” 2023). Recognizing that there are only specific strains that infect humans helps to narrow down the scope of how to combat each type. Plasmodium is a protozoa, a single-celled eukaryote, with four specific classifications that harm humans. While all of the four strains can infect humans, *P. falciparum*, the most dangerous, and *P. vivax* account for the majority of cases (Crutcher & Hoffman, 1996). Although many efforts focus more on these two strains, it is critical to address all four to ensure that they are all being combatted effectively.

Clinical Manifestations

Malaria does present with clinical manifestations, but the symptoms can sometimes be hard to distinguish from other illnesses and diseases. Some of the most common symptoms include: fever, chills, sweating, headache, and weakness (Crutcher & Hoffman, 1996). The fever caused by malaria, no matter the species of infection, is due to the rupture of mature schizonts (Crutcher & Hoffman, 1996). These ruptures may occur at different periods and timings, but they all result in a febrile period. The fever and other viral symptoms occur as a result of pro-inflammatory cytokines being released by the immune system (Halfalla et al., 2011). While some of these symptoms may seem like another illness, this disease can be severe and deadly.

Although malaria is curable, serious complications can arise from it which can be fatal. The most dangerous infection is from *P. falciparum* and if the diagnosis is delayed, the consequences may be cerebral malaria, severe anemia, and death (Crutcher & Hoffman, 1996). This occurs when the erythrocytes adhere to the endothelium of capillaries which can lead to circulation issues and anoxia within tissues (Crutcher & Hoffman, 1996). Ultimately, this leads to dangerous outcomes such as: cerebral malaria, renal failure, and GI bleeding, as well as other fatal repercussions of malaria. Cerebral malaria is one of the worst clinical manifestations of malaria. It occurs when the infected erythrocytes block the microcirculation within the brain, cutting off oxygen flow to the brain, a severe and fatal problem (Crutcher & Hoffman, 1996). These serious complications illustrate why it is important to catch malaria early for treatment.

Another serious concern with malaria is its effect on pregnant women, a highly susceptible population. Gestational and placental malaria can occur in many pregnancies in which the infected erythrocytes start sequestering within the placenta. This can result in preterm

deliveries, low birth weight, and higher infant and maternal morbidity (Halfalla et al., 2011). Specific treatments that are tailored for pregnant women will be discussed later in the paper.

The Life Cycle of Malaria

The life cycle of malaria is complex, especially since different stages occur in both the mosquito and human. In order to find weaknesses of the disease, understanding the way the parasite develops is vital. The life cycle is very technical and requires a strong understanding of cellular biology to fully grasp. However, one of the goals of this paper is to present a brief overview to provide the reader a cursory understanding of the disease. This overview will provide groundwork for a better understanding of why the PMI policy uses certain techniques to combat the disease at a biological level.

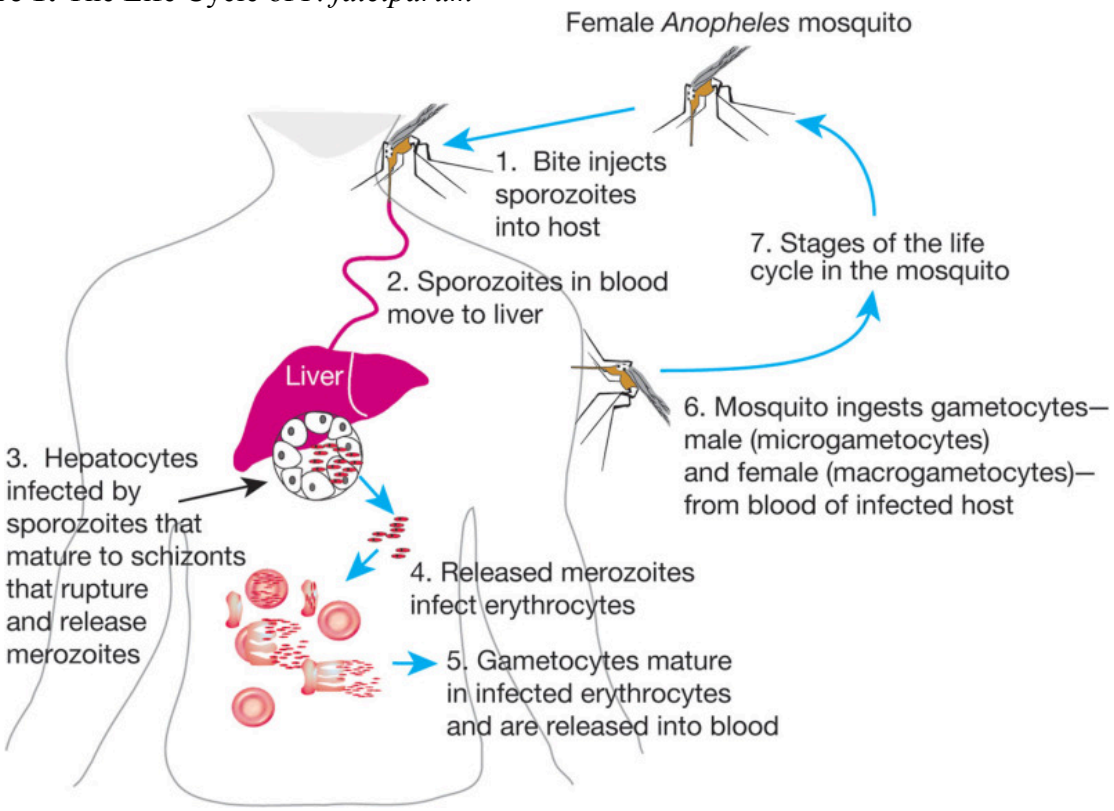
Table 1: Important biological terms related to the life cycle of malaria

Sporozoites	Part of the parasite that invades and infects liver cells
Schizonts	Division of infected cell
Merozoites	Invade and infect red blood cells
Red blood cells (RBC), erythrocytes	Carries O_2 to the body
Trophozoites	Active feeding stage
Gametocytes	Sexual stage
Zygotes	The combination of two gametocytes

An overarching, simplified life cycle of the disease is summed up well by the Centers for Disease Control and Prevention and is as follows (Centers for Disease Control and Prevention [CDC], 2020). The malaria-infected mosquito first bites a human during a blood meal and releases sporozoites. These sporozoites infect liver cells to mature and become schizonts. Once schizonts become mature, they rupture and release merozoites which travel through the human to infect erythrocytes, red blood cells. Once merozoites infect red blood cells, they go through asexual multiplication to become immature trophozoites, also known as the ring stage. At this point, there are two different pathways the trophozoite can undergo: the erythrocytic cycle (most common) or the sexual cycle. The erythrocytic cycle allows for the immature trophozoites to mature into schizonts, rupture and then repeat the cycle. The sexual stage is what perpetuates the disease. This is where the immature trophozoites mature into gametocytes (male or female) that are then taken up by the mosquito during a blood meal. Once inside the mosquito, the gametocytes combine to become a zygote which allows them to become motile ookinetes. When they gain motility, ookinetes invade the midgut wall of the mosquito, developing further into an oocyst. Oocysts then grow to ultimately rupture and release sporozoites that travel into the mosquito's salivary glands which then get released back into a human during a blood meal, continuing this multi-cycle life cycle.

The diagram below helps provide a simplified depiction of the life cycle, highlighting the important aspects of malaria development.

Figure 1: The Life Cycle of *P. falciparum*



Note. Varki et al. (2022). *Life Cycle of Plasmodium falciparum*.

There are some technical terms within this image that are key to understanding the mechanisms in biology. Sporozoites are the infective forms of malaria and develop when the malarial gametocyte enters the mosquito (Varki et al., 2022). The ookinete formed from the male microgamete and female macrogamete goes into the intestinal wall of the mosquito which results in an oocyst within the infected mosquito (Varki et al., 2022). This is an important step because the sporozoites, the biological component that infects humans, develop within the oocyst (Varki et al., 2022). Once the sporozoites are developed, they travel into the salivary glands of the mosquito that allows for them to be transmitted to humans when the mosquito bites the host

(Varki et al., 2022). The sporozoites are uninucleate and lancet-shaped, the infectious stage for humans (Crutcher & Hoffman, 1996).

The sporozoites injected from the infected mosquito travel to the liver through the bloodstream when they mature (Varki et al., 2022). When inside the liver, the sporozoites infect hepatocytes. The schizonts are spherical and multinucleate, a sign of the mature liver-stage of malaria (Crutcher & Hoffman, 1996). When this occurs, the sporozoites develop into schizonts which rupture and release merozoites (Varki et al., 2022). When the schizonts rupture, they don't just release a couple merozoites, they release thousands, somewhere between 2,000 and 40,000 (Crutcher & Hoffman, 1996). An important and dangerous part of malaria is in *P. vivax* and *P. ovale*, the maturation into schizonts within the liver parenchymal cells can be delayed up to one to two years (Crutcher & Hoffman, 1996). This is dangerous because it means that the infection within the human host can be delayed significantly thus making it harder to diagnose and treat.

These merozoites then go to infect red blood cells which provides the environment for gametocytes to mature and then be released into the bloodstream (Varki et al., 2022). The thousands of merozoites that are released can individually affect its own red blood cells, resulting in thousands of infected RBCs (Crutcher & Hoffman, 1996). Once within the bloodstream, it creates the cyclic nature of malaria as a mosquito that bites the infected host, ingests the gametocytes of malaria resulting in more mosquitoes acquiring malaria (Varki et al., 2022). Once the gametocytes enter the mosquito, it needs at least 2-3 weeks to develop into the sporozoite that can then go infect more humans, meaning that after a blood meal of an infected human, mosquitoes must live 2-3 weeks to become infectious (Crutcher & Hoffman, 1996). This has become an important part of prevention methods to try and reduce the lifespan of mosquitoes to prevent this development.

There are five steps that occur for a merozoite to infect a red blood cell. The first is there are ligands that bind the merozoite to the erythrocytes, bringing them into contact. From there, the merozoite then orients itself in a specific way so that its apical end is facing the blood cell, all with the help of ligands. An antigen (AMA1) moves to the merozoite surface which provides a junction allowing the merozoite to then move into the erythrocyte. While the specifics are unknown, a factor stimulates the actin-myosin motor which fully moves the merozoite into the red blood cell and forms a vacuole around the merozoite. The final step of the invasion is resealing the vacuole around the merozoite and the erythrocytic membrane that the merozoite just invaded through (Miller et al., 2013).

Once the merozoite infects a red blood cell, it has two pathways it can follow: maturation into an uninucleate gametocyte or into an erythrocytic stage schizont (Crutcher & Hoffman, 1996). The goal of the parasite is to continue reproducing and spreading, thus creating the need for a constant supply of gametocytes. The mechanism through which gametocytes develop from some of the blood stage parasites is still unknown and under research (Halfalla et al., 2011). As seen from this section, the malaria life cycle is complex and requires a serious understanding of it to properly target certain aspects of the parasite.

The Link Between Sickle Cell Anemia and Malaria

Another important biological aspect of malaria is its relationship to sickle cell anemia. Sickle cell anemia is a dangerous genetic disease characterized by the sickle shaped red blood cell resulting in dangerous clinical manifestations. This disease has been consistently linked to malaria and is important to understand because it helps provide a genetic background to some protective and harmful genetic traits in humans. Sickle cell anemia is caused by the homozygous

recessive presentation of the gene, HbSS. Sickle cell anemia causes a mutation in hemoglobin, giving it its recognizable “sickle” shape.

That being said, there have been protective features against malaria shown to be associated with a heterozygous individual for sickle cell anemia, presenting with the genotype HbAS. A C Allison was the first one to show that people in high malaria transmission areas have increased frequency of being heterozygous for sickle cell anemia and that it appeared to have some protective feature against malaria (Luzzatto, 2012). The protective mechanism discovered shows that when a red blood cell becomes infected by merozoites, the blood cell becomes a sickle shape (Luzzatto, 2012). There have been proposed reasons for why this happens to the blood cell, including the deoxygenation and lowering of the pH of the erythrocyte (Luzzatto, 2012). Once the red blood cell undergoes this sickling, macrophages then easily detect these misshapen cells and then undergo phagocytosis to stop the schizogony cycle of the parasite.

Furthermore, there has been increased research into the relationship between malaria parasitemia and host responses with sickle cell anemia to better understand the complex relationship between the two diseases. A recent research paper suggests that there are several proinflammatory cytokines and adhesins in children with sickle cell anemia and *P. falciparum* parasitemia (Henrici et al., 2021). The study concluded that children with sickle cell anemia and severe anemia exhibited decreased parasite burden when also infected with malaria (Henrici et al., 2021). This suggests that sickle cell anemia may change the immune response to malaria and presents new information that warrants further research.

A better understanding of how malaria and sickle cell anemia interact is important especially since it is a genetic feature frequently found in malaria endemic areas. Another

important part of sickle cell anemia is that it has been suggested that heterozygous individuals have “accelerated acquisition of immunity” (Luzzatto, 2012). This is still under debate, but may present as an important mechanism in the future to better understand innate immunity and whether it can be induced in individuals as a preventative measure. This may provide a unique opportunity for PMI to help lead research into developing a protective feature from sickle cell anemia.

At Risk Populations

While everyone living in a malaria endemic country is at a higher risk for contracting malaria, there are certain factors and situations that make certain populations more susceptible. Understanding this is important to ensure a policy measure effectively addresses individuals with higher risk of becoming infected. While it is important to protect the whole population, there are certain groups that are at higher risk for infection, thus warranting a greater focus of efforts to provide additional protection for them.

Malaria in Pregnancy

Every year, around 125 million women in malaria-endemic countries become pregnant, putting them at a high risk for contracting malaria and then suffering the complications that can arise ("PMI Technical Guidance," 2024). Within these millions who become pregnant, thousands fall to the mortality of malaria where around 10,000 maternal and 200,000 newborn deaths annually are due to malaria.

Women who are in their first or second pregnancy are more susceptible to the disease and also at increased risk for complications such as illness, severe anemia, and death. Pregnant women can experience these complications, but their babies can also experience some of the severe problems that can arise. This includes miscarriage, stillbirth, premature deliveries and low birth weight, all of which heavily contribute to child mortality.

Pregnant women are at a higher risk for infection because pregnancy can cause some loss of previous innate immunity ("What We Do," n.d.). The pathology of malaria within a pregnant woman is also different and increases the risk of negative consequences to the mother and baby. *P. falciparum* causes three specific changes in the placenta (Rogerson et al., 2007). The infected trophozoites can accumulate within the areas where maternal blood circulates which has been associated with preterm delivery (Rogerson et al., 2007). Furthermore, there may be more monocytes which have been associated with low birth weight and anemia (Rogerson et al., 2007). The last important change that *P. falciparum* causes within the placenta is that the malaria pigment, hemozoin, is present, indicating infection, and has also been associated with low birth weight (Rogerson et al., 2007). These outcomes are important to acknowledge because they help highlight why addressing pregnant women's preventative measures and treatment is crucial.

Children

Another dramatically affected population is children. Almost every minute a child under the age of five dies of malaria ("Malaria in Africa," 2024). This is a shocking and concerning number, highlighting a failure within malaria prevention methods. Children under five should not be dying at such high rates to a completely curable disease. In 2022, around 608,000 people died due to malaria. 76% of these deaths were children under five ("Malaria in Africa," 2024). Due to

the drastic number of infections and deaths, protecting children has become a key focus for prevention and treatment.

Children are more at risk because they are so young and have not yet developed any immunity to malaria. A level of immunity comes from exposure to the infection which allows the body to produce antibodies to protect from another infection. Since kids haven't been infected, they don't have any defense mechanisms to fight malaria. Another reason they are so at risk is because they have lost the maternal immunity that they had during the pregnancy and in the first couple months (Schumacher & Spinelli, 2012). Although maternal immunity remains relatively unknown, it is currently thought that antimalarial antibodies are transferred from the mother to the fetus, providing some degree of protection to the baby once born (Dobbs & Dent, 2016). Furthermore, the lack of protective immunity that comes from exposure over time, makes these young children especially susceptible to more dangerous and severe complications (Schumacher & Spinelli, 2012). The lack of protection that children have makes it critical to understand how to better safeguard children from malaria.

Even though malaria is so prominent within young children, it is very challenging to diagnose malaria as it can present like many other illnesses that also targets those under five. Common illnesses that it can be confused with are gastroenteritis, meningitis, and pneumonia (Schumacher & Spinelli, 2012). The lack of regularity within the presentation of symptoms is another challenge to diagnosing malaria and thus receiving the proper treatment. While there are generalized symptoms to look for when diagnosing malaria, every case is different and people may not present with all the symptoms that help lead to a diagnosis. An example of this is the presentation of a fever, especially in a specific pattern, is a key symptom that signals malaria. That being said, less than 25% of children with malaria present with this symptom illustrating

how challenging it is to diagnose childhood malaria (Schumacher & Spinelli, 2012). On top of that, there are other symptoms that build onto a malaria infection, creating more dangerous symptoms. This includes higher rates of vomiting and nausea than more mature individuals which can interfere with oral treatments (Schumacher & Spinelli, 2012). Kids have also been shown to complain less about chills and joint pain compared to their adult counterparts when infected with *P. vivax*, showing yet another issue with proper diagnosis in malaria within young children (Schumacher & Spinelli, 2012). This brief description of clinical manifestations within a high-risk population demonstrates how complicated this disease can be and why it is critical to properly understand the biology when drafting policy to combat it.

III. The U.S. President's Malaria Initiative

The main goal of this paper is to ultimately analyze certain aspects of PMI to determine whether or not it has effectively targeted the biology of malaria to realistically control and eliminate malaria from many endemic countries. In order to properly analyze this policy, it is important to understand the basis of the policy and the workings of it. This will help provide some background and critical information on the structure of the policy to help analyze the policy more in-depth later in the paper.

Policy Foundation

The U.S. President's Malaria Initiative (PMI) was developed in 2005 by Former President George W. Bush as an effort to combat worldwide malaria, especially in the most affected countries. His reasoning was as follows:

> We focus our attention on all who suffer from this terrible disease – especially the millions of the continent of Africa. We remember the millions more who died from this entirely preventable and treatable disease. As a compassionate nation, we are called to spread awareness about malaria – and we're called to act ("17th Annual Report," 2023).

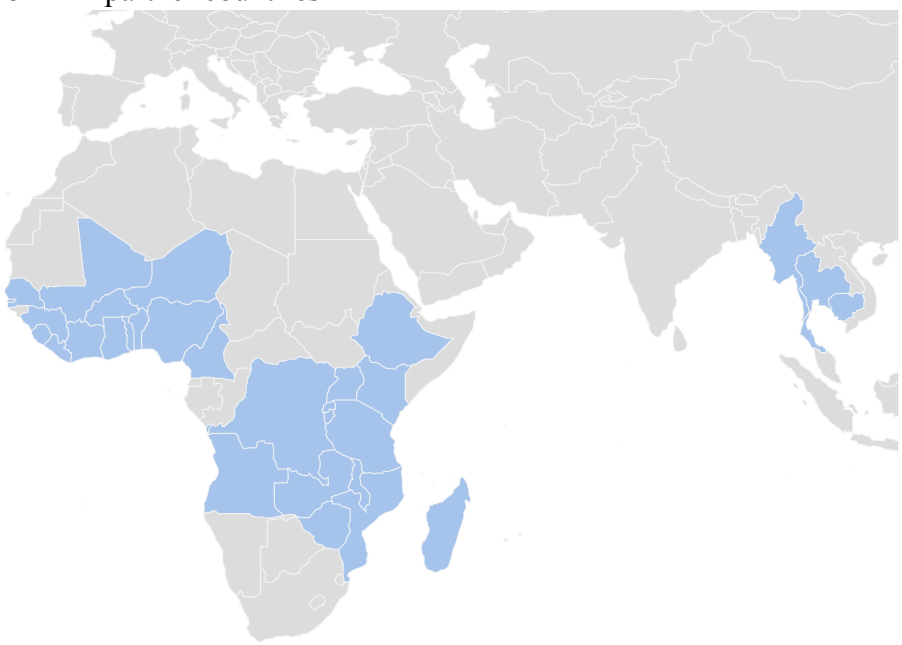
Former President Bush felt a moral obligation to step up and lead through foreign policy to drive malaria prevention in developing countries. The United States had effectively eliminated the disease in 1951, and yet dozens of countries are still fighting to contain malaria. This is a disease that has plagued the earth for decades, and while we're still far away from eradication, PMI has helped move the world in the right direction.

PMI is a multi-agency initiative that is led by the U.S. Agency for International Development (USAID) and supported by the U.S. Department of Health and the Centers for Disease Control and Prevention (CDC) ("End Malaria Faster," 2021). PMI receives its funding from USAID, all appropriated from the U.S. Congress specifically for malaria efforts. PMI started out with 15 high-burden partner countries to help provide support and resources for proven effective methods in malaria prevention and treatment ("About Us," n.d.). As the policy showed its global significance in the fight against malaria, it received more funding and resources through different partnerships. In 2008, the Tom Lantos and Henry J. Hyde Global Leadership against HIV/AIDS, Tuberculosis, and Malaria Act helped further PMI's impact by providing additional resources for more partner countries ("About Us," n.d.). Furthermore, it established the U.S. Global Malaria Coordinator as a Presidential appointee, further solidifying its importance in US foreign policy. These changes held PMI more accountable to the federal government and required comprehensive five-year strategies and annual reports to Congress. Not only did this signify that the United States was taking PMI seriously and considering it an

important health policy, it also reminded the policy group that they need to stay up to date in order to show that they are properly combating malaria.

As PMI continued to show how impactful they could be, they expanded the policy to four new countries in Africa along with a regional program in the Greater Mekong Subregion in Southeast Asia, particularly addressing antimalarial drug resistance within that population. In 2017, PMI added five new partner countries to get to the status of 24 countries and 3 programs in the Greater Mekong region ("About Us," n.d.). Within the last year, PMI announced that they are intending to partner with three new countries – Burundi, Gambia, and Togo. This shows that despite all the challenges that PMI faced with funding plateaus and COVID-19, it is remaining steadfast in its commitment to eliminating malaria by broadening its influence. The map below shows the current countries that work with PMI.

Figure 2: Map of PMI partner countries



Note. PMI (n.d.), *Where We Work*

There are a lot of reasons for malaria to remain a priority in the public health realm. Malaria takes a significant toll on the infrastructure of a country and can hinder its economic development. According to PMI, malaria can drain over a quarter of the income of affected families ("17th Annual Report," 2023). Not only does this affect the family and their income, it also affects a country's economic stability. When a large portion of their population is burdened with the financial responsibility of malaria, then that money is not available for the national economy. Furthermore, in certain countries where malaria is endemic, malaria treatment can account for up to 40% of national health spending ("17th Annual Report," 2023). This large portion of a country's funding can then hinder its spending on other health concerns and can divert a large amount of money away from other issues. In its 17th annual report to Congress, PMI brings up another crucial part of malaria to consider. When someone is sick with malaria, it affects their ability to attend to their everyday routine. For an adult, that can mean missing work and losing income to support their family and put back into the local economy. For children, that means missing out on school and negatively impacting their education. PMI also suggests that when kids miss the opportunity to go to school due to malaria, this then impacts the country's future by limiting the number of educated children in the country. Overall, PMI estimates that within some African countries that are heavily affected by malaria, GDP growth within the country can be reduced up to 1.3% each year ("17th Annual Report," 2023). Since GDP is a direct indicator of a country's economy, this statistic shows how significant of a negative impact malaria can have on a country's development. It suggests that by eliminating malaria, a country will regain some economic strength, highlighting the importance of targeting the disease.

Being an important US health policy, PMI is overseen and advised by a multitude of different groups. There is a specific advisory group made up of high-level representatives from

USAID, CDC, NIH, Peace Corps, State Department, Department of Defense, National Security Council, and other important US agencies ("About Us," n.d.). Including these important voices suggests that this is a policy that looks at all aspects of the disease. It recognizes that there is a serious need for the NIH and CDC to be a part of the discussion since malaria poses a biological health threat. Heavily incorporating the assistance of the NIH and CDC highlights the utilization of science agencies to provide support with combating malaria. This shows that PMI relies strongly on the biology of the disease as a way to properly target the disease. It also recognizes that the detrimental impacts that malaria can have on a nation can also be critical to foreign policy and national security. Acknowledging the importance of all these groups and giving them an opportunity to advise this policy, shows that PMI understands the true complexity of the malaria epidemic.

The 17th Annual Report to Congress by PMI highlights some of the important works this policy does and why it requires continual funding. PMI has helped save 11.7 million lives and prevent 2 billion malaria infections since 2000 ("17th Annual Report," 2023). That staggering number highlights the good PMI has done since its inception. Since 2006, the work PMI has done has helped decrease the rate of malaria cases by 27.2% and malaria deaths by 45.6% ("17th Annual Report," 2023). That is a major gain in the fight against malaria and shows the importance of PMI. When looking in the more recent years, in the 2022 fiscal year, PMI helped more than 700 million people with malaria prevention and/or treatment. Furthermore, PMI helped deliver 50.7 million mosquito nets, enough insecticides to spray 5.3 million homes, 48.1 million seasonal preventive treatments, 21.6 million preventative treatments in pregnancy, 94.9 million rapid diagnostic tests, and 80 million medicines for treatment ("17th Annual Report," 2023). That is a significant amount of prevention and treatment tools provided to its partner

countries. These are life-saving interventions that are crucial for helping these countries win against the fight with malaria. These statistics depict how impactful PMI is to the fight against malaria and its crucial place in the public health world.

Goals of PMI

For the first decade of PMI's existence, it was showing continually increasing positive results in helping control and eliminate malaria in its partner countries and regions. That being said, funding for malaria efforts has plateaued, resulting in a dangerous regression. According to WHO, "The population at risk for malaria has almost doubled since 2000 and global funding has plateaued, resulting in a $3.8 billion deficit in the amount the WHO estimated was needed to fight malaria just in 2021" ("WHO Guidelines for Malaria," 2023). Although the United States has been one of the main contributors in this fight, the slowdown in funding leaves some concerns for future malaria efforts.

Even though PMI has continued to be a leading policy in malaria control, the COVID-19 pandemic caused a setback in PMI's goals and its ability to positively impact its target countries. Between 2019 and 2021, PMI estimated that about 13.4 million malaria cases can be attributed to the disruptions caused by the pandemic ("17th Annual Report," 2023). As most of the world experienced, there were major issues with healthcare systems and overloading of infrastructure, even in developed countries. This resulted in issues with getting proper care and protection to those in need whether that be for COVID or other diseases, including malaria. Every five years, PMI releases its guidelines including goals for the following years and why they are highlighting those specific objectives. The pandemic disrupted the healthcare systems worldwide and halted malaria elimination progress. The health workforce, supply chains, and resources were

devastated by the pandemic and required a swift response from PMI. The policy quickly released a new strategy to address new threats and to continue making gains against malaria.

Following the pandemic, PMI unveiled its new strategy for 2021-2026, one that puts more emphasis on an individualized approach for each country to best target its needs. In its 17th Report, it highlights five key components: reaching the unreached, strengthening primary and community health systems, keeping malaria services resilient, investing locally, and leading and innovating. The five objectives provide a strategic approach to better address and eliminate malaria over the coming years.

Reaching the unreached focuses on tailoring their approach more towards those who are in remote and rural communities where services were lacking. This allows for a better and more situational approach that shows that every community can't approach controlling malaria the same way. Strengthening primary and community health systems refers to working more with the partner countries to take on malaria on a more community level. This includes investing more in the training of healthcare workers and helping supervising and providing the supplies and tools to be successful. In order to keep services resilient, this requires continued support and investment into local healthcare systems to ensure that when another health crisis occurs, it is better equipped and effective to address the issue. The complex and widespread challenges countries face including war, political instability, and other health crises, requires PMI to remain resilient and flexible to continue to combat health threats. Investing locally supports a country's own ability to tackle the challenges they face with malaria. The local community knows the best way to combat the disease, and by investing within these communities, it puts the leadership, decision-making, and implementation within these nations and strengthens their ability to combat the disease the best way they see fit. Malaria is a complex disease that requires constant

innovation and tools to properly eliminate the disease. By highlighting the importance of innovation, it acknowledges the constant need to keep up with every changing research front of malaria and how critical it is to keep flexible as new research and technology emerges. These objectives are important to acknowledge because it shows that through challenges PMI faces, it can quickly respond to them to keep its main objective of malaria elimination as its priority.

Local Voices on the Impact of PMI

Although it is important to understand the impact of this policy through statistics, it is also crucial to hear from those who are actually receiving support from PMI. It highlights the tangible ways that PMI affects everyday life while also showing its reliance on biology within communities. Learning more about the stories and legitimate impact PMI is having on its partner countries, helps acknowledge the important role PMI plays in the fight against malaria.

Nigeria is one of the most malaria-burdened countries, accounting for more than 25% of the world's cases ("Empowering Women," 2024). While everyone in a family can experience the hardships of malaria, women are more heavily relied on to provide support for the sick. They often have to take care of sick people: children, husbands, parents, etc. That is especially true in the Mbayen community in central Nigeria, a small area where women often have traditional roles ("Empowering Women," 2024). One woman in the community, Blessing Ichekula, recognized the greater risk for malaria infections women are placed into while farming, getting water, and cooking outdoors ("Empowering Women," 2024). After hearing about how women in many areas are at higher risk for infection, PMI created the Community Oriented Resource Persons (CORPS) in conjunction with the Benue State Primary Health Development Agency ("Empowering Women," 2024). This outshoot of PMI is made up entirely by women who work

closely with the health centers to ensure that the most high risk populations in their community, women and children, receive the care they need to remain safe, like intermittent preventive treatment in pregnancy and seasonal malaria chemoprevention for children ("Empowering Women," 2024).

Blessing Ichekula is one of the hundreds of women in CORPS who uses her training to ensure the safety of her community. She shares her training and knowledge to help educate and provide malaria services to Mbayen. Between September 2022 and September 2023, Blessing helped over 380 children. As being the only Mbayan representative, Blessing has the critical responsibility to make sure that the women and children know the resources available to them. She also shares the services at the closest health facility including free preventive medicine for pregnant women. CORPS is a program that empowers women, including Blessing, that highlights the critical role women play in reducing malaria infections. She is one story of many that is a testament to the strength of women. Although women are main proponents in this program, it also highlights PMI's ability to recognize gender-specific issues, and work with a local agency and community members to empower and strengthen communities in a lasting way. This is key for ensuring that malaria services and prevention will be continually talked about. Through putting the responsibility and strength within each community, it empowers them to advocate for the resources they need.

Ichekula's story highlights the importance of combining local advocacy of resources with treatments and preventative care. The resources that PMI helps provide are vital to the treatment and care of malaria, but they are useless without proper ways to share the information and help educate community members. PMI recognizes that empowering people in local communities is critical for its mission and to effectively combat the disease. This forward thinking aspect of the

policy demonstrates the power in uplifting local voices within communities to help educate others and ultimately provide them the resources needed to combat malaria.

Not only does PMI help empower local voices to share resources and help with prevention, it also helps empower the scientific community to help address the biological challenges of the disease. In 2022, Angola did not have the capabilities of independently conducting lab testing on mosquitoes to better understand malaria transmission within their country ("Empowering Angolan Scientists," 2023). Monitoring and tracking mosquitoes is a key aspect of PMI, one that shows the policy's understanding of the importance of addressing the biology of the disease. It is critical to track mosquitoes in areas such as entomological surveillance, response to insecticides, and resistance. That is because biology is the crux for eliminating malaria since that is how to truly target the disease. Without a thorough and constantly updated knowledge on malaria, it leaves countries vulnerable to mosquitoes adapting and overcoming some of the key prevention techniques. In 2022, PMI supported and provided the equipment and training needed to set up Angolan scientists to detect infective malaria parasites and molecular tests ("Empowering Angolan Scientists," 2023). Some of the important skills these scientists learned was how to prepare mosquitoes for molecular analysis, extract DNA, and later interpret test results to identify which species were present in certain areas ("Empowering Angolan Scientists," 2023). The support of local scientists broadened the local communities' ability to survey and try to stay ahead of the constantly evolving disease. One of the scientists, Julio Estobre, highlights just how important this training was, "with the right data at our fingertips, we can help better understand malaria transmission in Angola" ("Empowering Angolan Scientists," 2023). This story elaborates on how PMI acknowledges better

understanding of the biology malaria is critical for controlling its spread and protecting communities.

These stories help demonstrate the tangible benefits of PMI through local voices in different communities. As shown above, PMI stays actively involved in communities and helps strengthen the biological monitoring against mosquitoes. This is a vital part of maintaining proper surveillance on the biological workings of mosquitoes. Angola is just one of many stories that emphasizes how effectively PMI targets the biological mechanisms of malaria by persistently monitoring the disease to stay vigilant. Other voices such as Blessing Ichekula highlights an alternative approach to combating malaria, empowering local community members to help educate others on the disease and the different resources and treatments that PMI provides to combat the disease. Ultimately these stories show the different approaches PMI takes to effectively target the biological mechanisms of malaria and recognizing that multiple avenues need to be taken to combat it.

IV. The Biological Components of PMI

Sections I-III were aimed at providing some background information about the biology of malaria and the basis of PMI. That was to help with the analysis of the policy and the extent to whether it properly addresses the biology of malaria to properly eliminate and control the disease. Part IV will analyze specific parts of the policy that target the biology of mosquitoes and whether or not it is truly an effective way to combat malaria.

WHO is a leading international organization that helps set the standard for malaria interventions, which PMI bases the majority of its policy around. It uses insecticides and

treatments that are prequalified by WHO in order to ensure that it has been properly vetted by an outside source. PMI utilizes WHO as a guiding resource for implementing its prevention and treatment techniques. WHO has made it clear that it is absolutely crucial for multiple prevention and intervention techniques be used to avoid the development of resistant strains. Dr. Sunil Parikh explains exactly why, “We have to throw the kitchen sink at malaria. If you’re only doing one thing and resistance pops up, you’ve lost everything. But when you have multiple interventions out there, it protects the progress that we’re making” (“New Frontiers in Vector Control”, 2022). This highlights why PMI uses a multitude of different techniques to prevent malaria and why it is crucial for all these to be implemented. This shows why PMI takes on such a comprehensive approach to malaria efforts and why they target the parasite from all angles.

Insecticide Treated Nets

One of the cornerstones of the policy is the distribution and use of Insecticide Treated Nets (ITN). These are a literal physical blockade to mosquitoes, especially at night when they are most active and most likely to bite and infect people. Many studies have shown that high use of nets has helped reduce the number of infections. They have been proven to decrease child mortality, parasite prevalence, and malaria episodes ("PMI Technical Guidance," 2024). PMI holds this as one of the most important vectors to control malaria transmission and puts a strong emphasis on the need to continue the distribution of these nets. This physical barrier targets the size of the mosquito and its lack of mechanism to penetrate the net. Although a simple prevention tool, it is highly effective and an easy way to just stop mosquitoes from entering homes.

ITNs target both the physical size of the mosquito while also affecting the biological mechanisms within the parasite. ITNs have insecticides in them, which then attack the parasite on a cellular level to mitigate their transmission. There are three kinds of nets that are approved for use by WHO that incorporate different kinds of insecticides. Instead of just focusing on creating a physical barrier towards mosquitoes, PMI acknowledges that approach may do little to decrease the number of infected mosquitoes. By incorporating insecticides into these nets, PMI takes on a two-fold approach to try and combat the disease on multiple levels. The combination of these preventative techniques highlights the comprehensive approach PMI takes to properly combat malaria.

ITNs are a tried and true way of decreasing the spread of malaria. Data continues to show that they help reduce child mortality, parasite prevalence, and both uncomplicated and severe cases of malaria ("PMI Technical Guidance," 2024). Between 2001 and 2015, parasite prevalence in sub-Saharan Africa decreased around 50%. 68% of this decline can be attributed to the use of ITNs ("PMI Technical Guidance," 2024). These data show the critical importance of ITNs in this policy because it shows how dramatically it can decrease malaria transmission.

The three classes of insecticide-treated nets that WHO recognizes are as follows. The first is pyrethroid-only nets, those that kill mosquitoes that are insecticide susceptible. The next is using non-pyrethroid insecticides or using a pyrethroid insecticide plus a synergist. The goal of these nets is to kill the mosquitoes that have become insecticide-resistant. The last type of net is pyrethroid plus pyriproxyfen nets which aim to sterilize or reduce the reproductive capabilities of the mosquito. PMI tailors its approach to be more specialized for each region, taking a multitude of factors into account to distribute the appropriate nets, including entomology, epidemiology, and resistance data ("PMI Technical Guidance," 2024).

Pyrethroid-Only Nets

Pyrethroid nets have long been a standard for ITNs, but emerging data suggests that there has been an increase in pyrethroid-resistant strains. The pyrethroid only nets use one of the chemicals: alpha-cypermethrin, deltamethrin, and permethrin. Pyrethroids are 2250 times more toxic to insects compared to larger animals, such as humans, due to their more sensitive sodium channels (Chrustek et al., 2018). This allows for insects to be targeted, while not presenting high risks for humans.

Permethrin disrupts the voltage-gated sodium channels which increase the impulses causing paralysis and death in insects (Chrustek et al., 2018). Deltamethrin prolongs the opening of voltage-gated sodium channels causing hyper excitatory effects on insects (Chrustek et al., 2018). Alpha-cypermethrin disrupts the sodium ion transport in the cell membrane by keeping the sodium channel open causing continuous depolarization ultimately inhibiting the generation of action potentials (Chrustek et al., 2018). These three specific pyrethroids that PMI uses under this classification of nets help show the exact biological mechanisms that they target within the mosquito.

It is important to understand the ways these chemicals act on mosquitoes especially with the emerging data that shows increasing pyrethroid resistance. To combat this resistance, PMI tries to target different mechanisms within mosquitoes. The use of different pyrethroids in one classification of ITNs shows the broad range of insecticides used in just one prevention technique. Although similar in mechanisms to kill mosquitoes, it demonstrates the flexibility that PMI creates within its policy to make sure that at least one of these chemicals can be procured in its partner countries.

Non-Pyrethroid/Pyrethroid + Synergist

With the increasing amount of resistance in mosquito populations, another type of ITN that uses a synergist is piperonyl butoxide (PBO) which although not having its own insecticidal properties, enhances the potency of other insecticides ("PMI Technical Guidance," 2024). The combination of these chemicals works by inhibiting oxidase systems in mosquitoes. These systems are key mechanisms in which mosquitoes can break down insecticides and become resistant, making it an important part of their biology to target ("PMI Technical Guidance," 2024). The use of these synergists shows a way that PMI is trying to combat emerging resistance. It utilizes a separate chemical that, although not directly killing mosquitoes, targets a different mechanism that disrupts the mosquito's ability to become resistant. The creative use of a combination shows that PMI stays resilient to challenges and continues to problem solve to still target the disease at a biological level.

Dual Insecticide-Nets

Dual-insecticide nets use two active ingredients which both have insecticidal properties and are able to kill and/or inhibit mosquito reproduction ("PMI Technical Guidance," 2024). The use of two insecticides may help decrease the amount of resistance within a population. One common combination is alpha-cypermethrin (pyrethroid) and chlorfenapyr (slower-acting insecticide) which helps disrupt the energy production of the mitochondria within mosquitoes ("PMI Technical Guidance," 2024). This new net has been referred to as the Interceptor G2 (IG2) net. As discussed above, alpha-cypermethrin affects the sodium channels in mosquitoes to paralyze the insect through constant depolarization. Chlorfenapyr does not target the nervous

system like pyrethroids, it instead disrupts respiratory pathways and proton gradients in the mitochondria (Oxborough et al., 2015). This ultimately kills the mosquitoes by targeting them at a cellular level and stopping their respiration (Jamet, 2022). Chlorfenapyr is the slower-acting insecticide because it needs to be metabolized inside of the mosquito to become active, but also provides a novel and effective approach against malaria transmission (Jamet, 2022). The combination of these two insecticides targets different biological mechanisms of the mosquito, making it more vulnerable and less likely to develop resistance to both. Having an alternative to just one insecticide is important to counter increasing resistance and maintain the efficacy of ITNs.

Furthermore, multiple studies have suggested that the use of this net decreased malaria incidence significantly compared to pyrethroid-only LLINs (Jamet, 2022). Mozambique was one of the first countries to distribute IG2 nets, subsequently resulting in about a 50% reduction in malaria cases (Jamet, 2022). 50% is a staggering decrease in cases, showing why it is so critical to continue developing new prevention tools. Even people on the frontlines of the fight against malaria have seen firsthand the improvements of IG2. A doctor in Mozambique even claimed, “Hardly anyone comes to the clinic with malaria anymore… You don’t have to show me the data. I know that it has worked” (Jamet, 2022). This suggests that the increase of pyrethroid resistance is calling for a change in prevention tools due to the changing biology of the disease. It shows the promising results the new net has made and that there is a significant need for research to continue to evolve to keep targeting different mechanisms of malaria. The dual-insecticide nets represent another effective tool that PMI utilizes to target the biology of mosquitoes to control the population and try to reduce transmission.

Long-Lasting Insecticidal Nets (LLINs)

While ITNs are conventional, LLINs are an updated version that helps maintain the effectiveness of insecticides for up to three years. These nets are made one of two ways. The first incorporates the insecticide within the polyethylene net's fibers during production, which allows for a slow release over a long period of time ("Integrated Vector Management," 2017). The other type of construction coats a polyester net with resin and insecticide. This is an important transition as it demonstrates a desire to lengthen the lifetime of these nets to continue to disrupt the biological mechanisms within mosquitoes. The increased efficacy time has encouraged a push to move from ITNs to LLINs, showing the quick ability of PMI to transition with new research.

Although LLINs are an exciting new way to ensure longer efficacy of insecticides, it has also brought up new impacts to consider. LLINs do provide some reduced health risks which provides a strong argument for replacing all ITNs. LLINs reduces exposure during production because since it is factory produced, it no longer requires dipping the nets into the insecticides. This neutralizes one of the largest risks that ITNs pose to human health ("Integrated Vector Management," 2017). Furthermore, since insecticides are being woven into the nets to help with its slow release, it reduces some of the risk associated with physical contact ("Integrated Vector Management," 2017). This demonstrates that PMI is helping develop new ways to still target mosquitoes while also decreasing human risk and exposure.

In a USAID risk assessment, six active ingredients were tested reflecting the most used for insecticide nets. The overwhelming conclusion was that although there may be some adverse health effects, the efficacy of LLINs justifies its use. Four of the investigated chemicals contain

pyrethroids, where there are well established results on some neurological effects (“Integrated Vector Management,” 2017). However, this report also pushes back on some of these results by suggesting that the heightened risks of these chemicals may be overestimated. This suggests that there may be flaws in previous studies and that the tested chemicals may not be as harmful as they’ve said to be. The extensive research into these chemicals shows the comprehensive approach PMI uses to ensure that the insecticides they use are useful for targeting malaria, while also posing a minimal threat to humans. This shows a strong understanding of the biology of both humans and mosquitoes to select the appropriate insecticides to protect people while also targeting malaria.

Insecticide Environmental Considerations

Environmental considerations are an important part of foreign policies, especially when a vital part of the policy relies on heavy use of chemicals and insecticides. As important as it is to target the specific biology in mosquitoes, it is also critical to understand that there are often repercussions outside of the intended target. PMI does conduct extensive research and implement policies that address environmental concerns ("PMI Technical Guidance," 2024). Environmental considerations are critical to understand to ensure that the policy is doing more good than harm and holds PMI to a higher standard by ensuring that other implications of its mechanisms are considered.

ITNs have an active life of around three years, and require proper disposal to ensure minimal environmental impacts. That being said, collection of inactive ITNs is not that high up on PMIs priorities so they instead set forth guidelines for repurposing and what not to do with the old nets. Furthermore, PMI has identified different classifications for repurposing ITNs as

beneficial, neutral, or misuse. A beneficial use of old ITNs is using these nets still to block mosquitoes whether that be patching active nets, stuffing eaves and other ways to prevent mosquitoes from getting in. A neutral use includes no longer using the inactive net for preventing mosquito bites, but using it in a way that doesn't have any negative impacts. This may include using them to transport crops, make soccer nets, or as fencing. Although they may no longer be used as their original intended purpose, they are still being used in a beneficial way that poses no threat to the environment or those using them. The last classification is misuse, where the nets are not being used for mosquito bite prevention and also using them in a way that harms the environment. This includes using them as fishing nets. ITNs have been shown to poison aquatic life, posing a direct threat to the environment and thus highly discouraged.

Although some of the insecticides may pose a threat to the environment when misused, they do all go through a thorough vetting process using USAID's integrated vector management programs. The Programmatic Environmental Assessment has discovered that the insecticides used show a low risk for negatively affecting humans and the environment. The additional precautionary measures PMI takes to ensure the safety of the insecticides they procure shows its commitment to not only targeting the biology of malaria within mosquitoes, but also to the environment to ensure that the main effect of ITNs is to disrupt malaria transmission.

Side Effects of ITNs

The use of ITNs would be irrelevant if the chemicals used to kill the mosquitoes were harmful to humans. However, the chemicals the PMI uses have extremely low human toxicity. They are even safe enough that a baby sucking on the net would not be harmed ("PMI Technical

Guidance," 2024). This is an important consideration and shows that the chemicals used by PMI are tailored to target the biology of mosquitoes and not have negative consequences for humans.

Although overall the insecticides used pose minimal risks to humans, there may be some minor side effects such as skin and membrane irritation with the use of alpha-cyano pyrethroids. That being said, this occurs only when removing the nets first from its packaging. PMI has already addressed these issues by encouraging workers to stop handling ITNs once experiencing symptoms and educating them that these effects are temporary. Furthermore, certain countries have advised citizens to let ITNs air out for a day before use. PMI continues to show a strong commitment to combating malaria while also ensuring the safety of community members and staying up to date on public health research.

Indoor Residual Spraying

Another preventative technique PMI uses is Indoor Residual Spraying (IRS) which treats the interior walls of homes with a long-lasting insecticide that helps kill mosquitoes ("What We Do," n.d., PMI). This has proven to be an effective preventative measure that kills mosquitoes and disrupts malaria transmission. In order to protect communities, at least 80% of houses must be sprayed to ensure that mosquitoes are properly targeted and disturbed ("What We Do," n.d., PMI). This is another important method that PMI uses to target the biology of mosquitoes to ultimately kill them and reduce malaria transmission.

The goal of IRS is to target mosquitoes when resting on surfaces before or after a blood meal by using insecticides that kill them. These insecticides kill the mosquito between 24-72 hours after contact with the chemicals. This reduces the lifespan of the mosquito and critically

shortens it to the point where the mosquitoes cannot develop the parasite's lifespan. This means that it will no longer live long enough for the parasite to continue its development thus decreasing the spread of the parasite ("Integrated Vector Management," 2017). This is absolutely necessary to reduce transmission rates because if the vector for the malaria parasite dies, then the mechanism for the disease to proliferate is stopped short. PMI's emphasis on IRS demonstrates its understanding of the importance of targeting the mosquito lifespan as a way to decrease the development of malaria. This shows its reliance on the biology of malaria and one of its hosts to try and stop its growth and further transmission.

Insecticide Selection

PMI relies heavily on the use of IRS as a way to protect the population by spraying homes and buildings with specific insecticides. That being said, PMI recognizes that every location differs so the approach to each setting should be taken into account to determine the best insecticide to use for the IRS. That means that one insecticide may not be the best one to use in every location, and there needs to be careful consideration to select the correct chemical. In order to make the best decision, PMI specifically looks at the vector susceptibility/resistance status, duration of efficacy, the use of ITNs in the IRS targeted area, and cost ("PMI Technical Guidance," 2024). In order to determine which insecticides should be used, experts are consulted at least nine months prior to the spray campaign. This includes meeting with operational and entomology leads, partners, and the working groups within the country to ultimately determine which is best for the situation ("PMI Technical Guidance," 2024). The extensive background and research that goes into insecticide selection shows the strong desire of PMI to target malaria in

all locations and the need for a tailored approach in order to combat the disease effectively at a cellular level.

PMI restricts the use of IRS to five chemical classes, all backed by WHO. These all target different mechanisms within mosquitoes to stop the growth of malaria within. The table below lists the categories including some of the advantages and disadvantages of each one that factors into decisions.

Table 2: IRS insecticides used by PMI

Chemical class	Advantages	Disadvantages	Cost/sachet or sachet equivalent
Pyrethroids	• Low toxicity • Low cost • >7 months duration for longer-lasting formulations	• Resistance • Used in majority of ITNs	$2-3
Carbamates (Brand name: Ficam)	• Medium toxicity • Less resistance	• Higher cost • < 4 month duration	$11*
Organophosphates** (Brand name: Actellic)	• Less resistance • CS formulation >6 months duration	• Higher relative toxicity • Higher cost	$16
Organochlorines (DDT)***	• Low cost • >7 months duration	• Management costs • Resistance • Supply	$4-$6.70
Neonicotinoids** (Brand names: Fludora Fusion, 2Gard, SumiShield, Klypson)	• Less resistance • Residual efficacy up to 10 months	• Higher cost	$14.50

*The number of structures sprayed per bottle/sachet is approximately equivalent for all insecticides, however, the short residual life of current WHO-recommended carbamate formulations means that in areas of year-round transmission, two rounds of spraying are required, effectively doubling the price of carbamates.
**Currently all PMI-supported spray programs utilize the organophosphate and/or neonicotinoid classes of insecticide.
*** DDT does not currently have a WHO PQ recommendation

Note. PMI (2024), *Advantages and Disadvantages of IRS-Recommended Chemical Classes*

To better understand why PMI would choose one of these insecticides over the other, it is important to learn about how each of these insecticides works at a cellular level to kill

mosquitoes and ultimately disrupts the development of malaria. While they all may have different targets and mechanisms, all five classes are neurotoxins which paralyze and kill the mosquito that lands on surfaces covered with them ("PMI Technical Guidance," 2024). PMI's comprehensive list of insecticides used in IRS show the overwhelming commitment to targeting malaria on a cellular level as a mechanism to control the disease. The following paragraphs will delve deeper into the actual workings of these insecticides and exactly how they kill mosquitoes.

The first of these classes is organochlorines (DDT) which has been used for years for a multitude of different purposes. It was used heavily in World War II, but then became banned in the United States and other countries due to its negative environmental effects ("Integrated Vector Management," 2017). It is only recommended for use in emergency cases for malaria control. Since this chemical has been used for such a long time, lots of the research on mosquitoes was determined back in the mid 1900s. This chemical acts on the mosquito's neuron sodium channel which prevents nerve impulses to recharge ("PMI Technical Guidance," 2024). This ultimately results in the mosquito's death because it cannot properly recover from nerve impulses. The extreme environmental impact of DDT makes it less used than others and usually not the first choice for PMI.

Carbamates and organophosphates on the other hand inhibit acetylcholinesterase activity which terminates the action of acetylcholine at nerve synapses ("PMI Technical Guidance," 2024). This results in the accumulation of acetylcholine, which continually excites the neuron causing hyper excitatory effects. Carbamates bind loosely and can be reversed while organophosphates bind much stronger meaning that organophosphates can't be unbound easily by the insect.

Neonicotinoids mimic acetylcholine and bind to its receptor. This causes high levels of activation and overstimulation to the insect ("PMI Technical Guidance," 2024). This is a slower acting chemical, killing the mosquito within 72 hours, instead of the 24 hours of the others. Since the mortality of the insect comes much later than other insecticides, it requires more extended monitoring which can be challenging for certain countries to fulfill.

A sixth potential class remains under review, but pyrroles may have an important role in the future because they are not neurotoxins. That being said, pyrroles disrupt the mitochondrial ATP production within the insect's cells ("PMI Technical Guidance," 2024). The one pyrrole that is being used in ITNs is chlorfenapyr, which is still under review for its use in indoor residual spraying. Since ATP is vital for insect function, the disruption of this mechanism results in cell death and ultimately insect death.

This list of insecticides is meant to show the cellular workings of each of the chemicals used by PMI for IRS. It helps highlight why the IRS is so effective and that each of these classes provide a beneficial mechanism for killing mosquitoes. This is also a way to illustrate the extensive amount of ways PMI uses to combat malaria on a cellular level.

Proper Insecticide Rotation

Not only is the proper selection of insecticides relevant to reducing transmission of malaria, it is also key to maintaining proper insecticide rotation. Malaria has shown to be so persistent because the parasite can become insecticide resistant. Its ability to become resistant to these insecticides requires a tailored approach to ensure that the ones being used remain effective. PMI recommends a phased approach with an ideal length of one year rotations but also

acknowledges that two years can be used for practicality ("PMI Technical Guidance," 2024). The golden rule is that don't use insecticides back to back if they have a similar target site because that may not rotate it enough to combat resistance. This is why it is important to have an understanding of the mechanisms of each insecticide, to ensure that the rotations are staying on track to target different cellular processes. The combination of research into each chemical and the need for proper rotation shows another two-fold approach PMI takes to continue to target malaria effectively on a cellular level.

Pregnancy

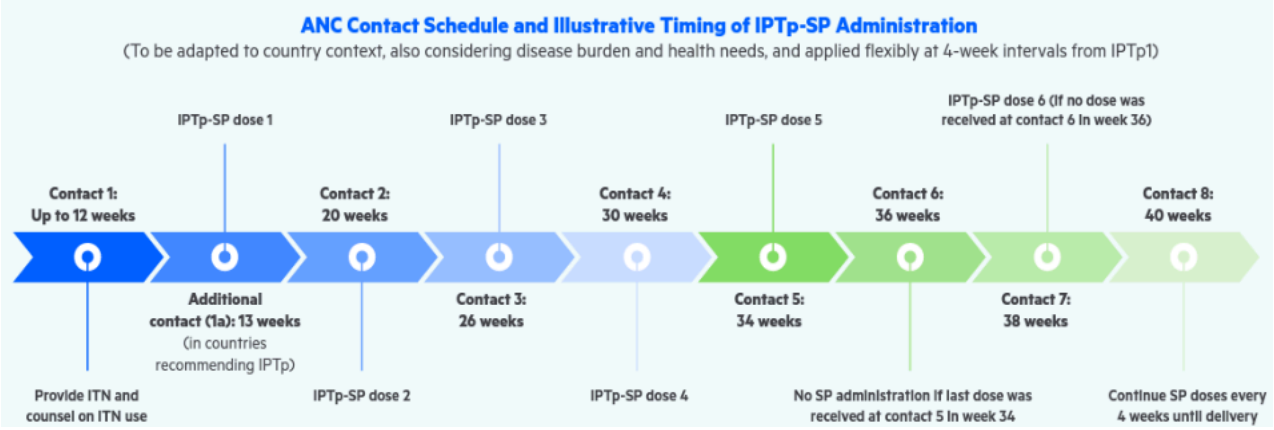
While ITNs and IRS remains an important technique for protecting all community members from malaria, it is also important to acknowledge that there are higher risk populations that need more attention for protection. One of the highest risk populations as discussed previously is pregnant women. The severe complications that a malaria infection can cause has led to a push in ways to protect these women to help both themselves and their baby. This requires a more specialized approach that benefits the woman and baby by preventing an infection from infected mosquitoes and not causing other serious repercussions. PMI recognizes the hard balance between the two and takes proactive steps to try and address malaria in pregnancy from several angles: prevention and treatment.

Antenatal Care (ANC)

Antenatal Care (ANC) is a crucial part of reducing malaria throughout a pregnancy and is a key aspect of PMI's fight against the disease. It allows for pregnant women to be continually monitored and checked-on throughout the pregnancy to help ensure fewer complications. This

simple precaution is absolutely critical for preventing malaria and targeting the disease. Furthermore, it is also a key platform to deliver intermittent preventive treatment in pregnancy (IPTp) consistently. The recommendations for ANC visits and treatment are shown in the diagram below:

Figure 3: PMI recommended timeline for IPTp



Note. PMI (2024), *PMI technical guidance*

Intermittent Preventive Treatment in Pregnancy (IPTp)

One of the most important ways to protect pregnant women is the use of IPTp. This treatment is periodic dosing of pregnant women with an antimalarial drug regardless of whether they have detected parasitemia ("PMI Technical Guidance," 2024). The ultimate goal of this program is to decrease parasites in the placenta to provide protection to the mother. The main reason that it is given no matter the state of parasitemia is because it is not always detected even if it is present, so this provides protection in the case that it goes without detection. This is a simple treatment that plays a big part in disrupting the development of the parasite to protect the woman and baby.

WHO recommends one regimen, the use of sulfadoxine-pyrimethamine (SP), the only combination shown to be safe and effective. Each dose is composed of three tablets, each consisting of 500 mg sulfadoxine (1500 mg total) and 25 mg pyrimethamine (75 mg total). A benefit of this drug is that it can be given with or without food, making it easier to remember to take since there are fewer restrictions on usage. WHO recommends that SP should be administered every antenatal care visit after the first trimester and can be given as often as monthly following the first dose ("PMI Technical Guidance," 2024). Sulfadoxine-pyrimethamine inhibits the folate metabolic pathway, a key part of the parasite's mechanism of action (Hyde, 2005). Folate is key for DNA synthesis and creating other important enzymes so by inhibiting that pathway, the parasite cannot survive (Metz, 2007).

There are always limitations with drugs and some concerns about the efficacy of SP have been raised after not showing efficacy in children. However, there has been research suggesting that a pregnant woman's pre-existing immunity helps amplify SP. Since children don't have this immunity, that is why it has been shown to not be an effective tool ("PMI Technical Guidance," 2024). Therefore, SP remains a viable treatment for pregnant women as a mechanism of limiting parasitemia.

PMI studies and reports suggest that in areas where IPTp is being used, malaria has been reduced significantly ("PMI Technical Guidance," 2024). This method for prevention during pregnancy is the most effective with prevention and cost than any other alternative. Other methods such as Intermittent Screening and Treatment in Pregnancy (ISTp) show to be more costly and less effective because it does not catch every single case ("PMI Technical Guidance," 2024). ISTp includes receiving a rapid diagnostic test at each ANC visit and only treating those

who test positive. As mentioned previously, parasitemia does not always show up on these diagnostic tests, thus making it less accurate in detecting cases.

There are some guidelines to ensure its efficacy including not taking daily folic acid above 5 mg and not being on cotrimoxazole prophylaxis, a treatment for HIV-positive individuals (Grimwade & Swingler, 2003). Folic acid is important for the DNA synthesis and thus survival of malaria parasites (Metz, 2007). Furthermore, it can also work as an antagonist to antimalarial drugs and promote plasmodial growth (Metz, 2007). Folic acid is a common supplement for pregnant women so it is important to make sure that women know the effects it has in conjunction with antimalarials. This poses a challenge because Sub-Saharan Africa has the highest rate of HIV infections as well, so having limitations on prenatal care based on one of the HIV treatments shows a flaw in SP regimens. That calls for a need for PMI to continue researching and developing another preventative treatment for pregnant women to make it more accessible for those also infected with HIV.

Treatment of Malaria in Pregnancy

While IPTp does help with the prevention of lots of malaria cases, it is not perfect and there are still positive diagnoses in pregnant women. There are specific guidelines for treatment within pregnant women since there are more considerations with the biology of pregnancy.

The following PMI table outlines the current recommendations for treatment for malaria during pregnancy put forth by PMI.

Table 3: PMI Recommended Treatment of Malaria in Pregnancy

	1st trimester	2nd or 3rd trimester
Uncomplicated malaria	Artemether Lumefantrine (AL)**	ACT*
Severe malaria	IV/IM artesunate (preferred) or IV/IM quinine if artesunate not available	IV/IM artesunate (preferred) or IV/IM quinine if artesunate not available

* HIV infected individuals on zidovudine or efavirenz should avoid ACT regimens that contain amodiaquine.

Note. PMI (2024), *PMI technical guidance*

To better understand why PMI uses these treatments and whether or not it is effective, it is necessary to understand the cellular mechanisms of the drugs to combat malaria. Artemether Lumefantrine (AL) works by targeting multiple mechanisms within the parasite. Artemether has been shown to interfere with plasmodial transport proteins, the electron transport chain, and production of free radicals (Stover et al., 2012). It also increases parasite clearance. Lumefantrine has less research on its significance, but it is thought to inhibit β-hematin formation which is a detoxification pathway in malaria (Stover et al., 2012). Lumefantrine is also a slower onset drug thus decreasing the rate of a recurrent infection (Stover et al., 2012). The combination of these drugs provides a "complementary pharmacokinetic-pharmacodynamic profile" which has been suggested to have good success rates (Stover et al., 2012).

Artemisinin-Based Combination Treatment (ACT) is considered the gold standard for uncomplicated malaria cases. Its efficacy and mechanisms will be discussed later in the paper.

IV/IM artesunate targets the young, ring-stage parasites which has been associated with faster parasite clearance compared to quinine. Some studies have suggested that artesunate increases cure rates, lowers gametocyte carriage and decreased treatment failure (Kovacs, Rijken, and Stergachis, 2015). Artesunate is considered to be a more effective treatment for malaria, but quinine can be used if needed.

Malaria and HIV

An important consideration PMI must take into account is the relationship between HIV, pregnancy, and malaria. HIV is very prominent in Sub-Saharan Africa and thus demands strong consideration when treating malaria. An important consideration is that HIV increases risk and intensity of malaria ("PMI Technical Guidance," 2024). For example, an HIV infection reduces a woman's ability to control a *P. falciparum* infection, decreases her response to antimalarial treatment, and increases risk for malaria-associated adverse birth outcomes ("PMI Technical Guidance," 2024). For those reasons, it is critical to address the possibility of both of these infections being present in a pregnant woman.

IPTp remains a critical preventive tool for HIV-infected women when they are not receiving trimethoprim-sulfamethoxazole (cotrimoxazole) prophylaxis. This is because the use of both increases the risk for adverse effects. Furthermore, daily use of cotrimoxazole provides similar protective effects of IPTp if the doses aren't missed ("PMI Technical Guidance," 2024). This is all to say that it becomes even more important for these women to receive ITNs/LLINs to sleep under during pregnancy to reduce their risk of contracting malaria.

Children

Another high-risk population that PMI takes more precautions with is children. Children die from malaria infections at a staggering rate. As mentioned in the introduction section, almost every minute a child dies from malaria. To say that malaria is dangerous in children is a drastic understatement. The fact that children are so heavily affected calls for increased attention to how to protect and prevent malarial infections within these groups.

Seasonal Malaria Chemoprevention

One way that PMI tries to help protect children from malaria is the use of seasonal malaria chemoprevention (SMC). SMC is "the administration of treatment doses of longer-acting malarial medications at monthly intervals in areas of exclusively seasonal transmission with the aim of maintaining protective drug concentrations in the blood throughout a complete season of peak transmission" ("PMI Technical Guidance," 2024). The idea of SMC is to try and reduce the malaria burden by giving children in high risk age groups antimalarial drugs during peak transmission seasons to clear existing infections and prevent new ones (WHO, 2023). This is only recommended in areas with highly seasonal *P. falciparum* transmission, but has been effective when implemented.

Sulfadoxine-pyrimethamine plus amodiaquine (SPAQ) is recommended for children between 3-59 months every 28 days during peak transmission periods. It is also only recommended for when 60% of malaria cases occur within about four months each year (WHO, 2023). Currently PMI is not supporting SMC with SPAQ in Southern Africa because there is well documented SP resistance ("PMI Technical Guidance," 2024). SPAQ is used because it has been shown to provide a high degree of protection for up to 28 days which is critical during high transmission times (WHO, 2023).

When SMC is used, studies have shown that it has been highly effective as a preventive treatment. It has prevented around 75% of all malaria episodes and can reduce around ⅓ of incidence of moderately severe anemia (WHO, 2023). SMC is effective but there needs to be a consideration regarding parasite resistance to the drug. While a useful tool, it needs to be

implemented sparingly and only when needed to ensure that mosquitoes do not develop resistance to this important preventative tool.

Vaccines

Although all the previously mentioned prevention and treatment techniques are vital for controlling malaria, vaccines are going to be a crucial next step to truly eliminate it. PMI has been crucial in helping develop and distribute a new vaccine in the fight against malaria. The dedication to creating a vaccine shows the strong commitment PMI has towards the biological aspects of prevention. In the past couple of years, scientists have been working hard to produce an effective vaccine, and in 2021, the WHO announced a groundbreaking recommendation, the widespread use of the RTS,S/AS01 vaccine for children in Sub-Saharan Africa and other areas with moderate to high *P. falciparum* transmission.

The RTS,S/AS01 vaccine targets the circumsporozoite protein. This induces antibodies associated with the prevention of *P. falciparum* infection which provides protection for the vaccinated individual (White et al., 2015). This vaccine is considered to be a pre-erythrocytic recombinant vaccine because it targets the parasite before it infects the liver cells (Laurens, 2020). This vaccine has been a long time in the making. The circumsporozoite protein (CSP) antigen was discovered decades ago, but took a long time to discover its significance to combat malaria. The RTS,S/AS01 vaccine was created when the CSP central repeat was added to hepatitis. This was then added to the CSP C terminal region, ultimately creating the vaccine (Laurens, 2020). This created the name of the vaccine: “R” = central repeat region, “T” = T-lymphocyte epitopes, “S” = the surface antigen of Hepatitis B that the RT portion fuses to, and the final “S” = unfused HBsAg that spontaneously fuses with the RTS portion (Laurens, 2020).

Research and development on a vaccine has been years in the making, dating back to 1893. Before the WHO recommended its use, the vaccine did undergo extensive clinical studies. The phase III trial included children between 5-17 months old receiving a 4-dose regimen ("PMI Technical Guidance," 2024). The trial suggested that despite low to moderate-efficacy, it did help avert a high number of cases and thus warranted further testing. That led to a large-scale pilot implementation project to better understand the feasibility of the vaccine and its impact on mortality. Ghana, Malawi, and Kenya participated in this study and ultimately came to the conclusion that the RTS,S/AS01 vaccine should be implemented in other countries ("PMI Technical Guidance," 2024). The pilot use of the RTS,S/AS01 vaccine showed a 13% drop in mortality among children who were eligible to receive the vaccine (“The RTS,S Malaria Vaccine,” 2023). Although 13% seems small for such a groundbreaking vaccine, when put in perspective that over 450,000 children die from malaria a year, it shows that it saves thousands of lives annually (“The RTS,S Malaria Vaccine,” 2023). Furthermore, it is estimated that around one life is saved for every 200 children vaccinated, a huge success for protecting children (“The RTS,S Malaria Vaccine,” 2023).

The results of trials and studies have revealed its significant impact on populations. There was a significant reduction in clinical malaria (51%) and severe malaria was down 45% after 12 months of the first three doses ("WHO Guidelines for Malaria," 2023). It is going to be important to monitor the rollout of the vaccine in the upcoming year when PMI’s partner countries are scheduled to receive many of their clinical doses. While an exciting step in the right direction, it is still vital to ensure that other prevention tools are still in place and that the efficacy of the vaccine is truly monitored to ensure that it is a safe and effective tool moving forward.

Community Significance

Not only has PMI helped distribute and deliver this groundbreaking new vaccine, it has been crucial for its development. Professor Kwaku Poku Asante works at the Kintampo Health Research Center (KHRC) in Ghana and his team has been one of the main leaders in conjunction with WHO to develop and research malaria vaccines ("A Scientist Behind Vital Research", 2024). KHRC provided some key contributions into the efficacy and safety of the RTS,S vaccine that enabled them to work closely with WHO to look at the vaccine specifically in Ghana.

Asante grew up in Ghana and saw the effects malaria had on his community both as a child and when he became a clinician. He witnessed the high burden of malaria on his country and especially the children and families which is what drove him into malaria epidemiology ("A Scientist Behind Vital Research", 2024). As he gained experience, he found that six out of ten children had malaria parasites and anemia was also high within children. People within the high malaria burden countries experience the impact the disease has on their country, and PMI helps support these people to become leaders in their community and encourage them to join the fight against malaria.

Professor Asante and his team are now helping lead research into the efficacy of implementing the vaccine with other prevention tools already in place ("A Scientist Behind Vital Research", 2024). This is critical work to ensure that the vaccine is not interfering with any other prevention techniques used by PMI. Professor Asante is just one story that shows how PMI is encouraging and empowering scientists within its partner countries to do vital research that is paving the way for important biological advancements.

Diagnosis and Treatment

Although focusing on some high risk populations is critical for protecting those groups, it is also important to have an overarching policy that can be applied to any community member. An absolute key part of controlling malaria is diagnosing and treating the disease, thus also being an important part of PMI. It is important to continue to test for malaria in order to treat it as soon as possible. Treatment includes focusing on two main objectives: curing the acute blood stage and clear hypnozoites from the liver to prevent relapses ("WHO Guidelines for Malaria," 2023). PMI uses rapid diagnostic tests (RDTs) and microscopy to test for malaria and then treat those that come back positive.

Rapid diagnostic tests (RDT) detect the presence of *Plasmodium*-specific antigens in the blood ("PMI Technical Guidance," 2024). These tests detect the antigens histidine-rich protein 2 (HRP2), *Plasmodium* lactate dehydrogenase (pLDH), or aldolase ("PMI Technical Guidance," 2024). There are different tests whether they test for one antigen, multiple antigens, or multiple species, but all are meant to detect whether a malaria infection is present. Since RDTs do not detect the density of parasitemia, they are not used in to manage severe malaria and can also test positive even if the parasites have been fully cleared for up to two weeks ("PMI Technical Guidance," 2024).

The recommended course of treatment for uncomplicated malaria is the use of Artemisinin-Based Combination Treatment (ACT). This regimen utilizes an artemisinin drug combined with a second antimalarial ("PMI Technical Guidance," 2024). Artemisinin is used because it rapidly reduces the parasite density in the bloodstream (high killing rate) while also helping control some of the symptoms, especially fevers ("PMI Technical Guidance," 2024).

When that gets paired with a longer-acting antimalarial, it helps address some of the immediate symptoms and issues, while also helping maintain parasite clearance later on. Furthermore, the use of two drugs in treatments is a common principle for other illnesses such as tuberculosis, HIV, and different cancers (Nosten & White, 2007).

Over a three-day treatment, ACTs target two asexual malaria cycles which reduces the number of parasites by around one hundred million-fold. It also has gametocytocidal activity which further decreases malaria transmission (Nosten & White, 2007). Artemisinin works against blood and early gametocyte stages of *P. falciparum* (Adebayo et al., 2020). There have been lots of data suggesting a strong emergence of resistant strains towards artemisinin, threatening one of the core treatments. That's when WHO shifted to encourage combination therapies, which combines the fast-acting artemisinin derivatives with a slower acting antimalarial (Adebayo et al., 2020).

Artemisinin and its derivatives have a short half-life of about an hour (Nosten and White, 2007). This makes them a significantly quicker antimalarial drug than other options. The derivatives of artemisinin all convert to dihydroartemisinin, a more potent antimalarial, *in vitro* (Nosten & White, 2007). One of the main ways this antimalarial works is by targeting the young ring form parasites and preventing their development to more mature stages (Nosten & White, 2007). There are other proposed mechanisms for its function including inhibiting the "polymerization of heme, production of free radicals and alteration of membrane transport properties of the malaria parasite, which inhibits the nutrient flow in the parasite" (Adebayo et al., 2020).

Heme is a molecular component of hemoglobin, the oxygen carrying molecule in the blood. It is thought that the artemisinins prevent hemozoin formation which results in the accumulation of heme, a toxic substance to malarial parasites (Adebayo et al., 2020). *P. falciparum* uses hemoglobin as a nutrient source, so by impairing its ability to digest it, it renders one of its important sources useless. Another important mechanism artemisinin disrupts is the parasite membrane. When heme builds up, reactive oxygen species (ROS) are generated which causes oxidative damage on the parasite's membrane, killing the parasite (Adebayo et al., 2020).

There are six different combinations of ACT that can be used and recommended to be selected based on the expression of resistance in the area. Each of the compounds in the drugs target cellular mechanisms within the mosquito. The following paragraph gives a quick description of each compound and is then followed by a table which sums up the differences amongst them.

Artemether-lumefantrine (AL) works against all human malaria parasites and even some drug-resistant strains (Nosten & White, 2007). In artesunate-amodiaquine (AS-AQ) amodiaquine has schizonticidal and gametocytocidal activities and is effective against chloroquine-resistant strains (Adebayo et al., 2020). It also has a longer half-life than artesunate, making it a longer-acting antimalarial. SP-AS is a combination of sulfonamide and pyrimethamine which are synergists against the malaria parasites (Nosten & White, 2007). Sulfadoxine-pyrimethamine helped decrease the asexual parasite density and also presented with gametocytocidal properties (Adebayo et al., 2020). Mefloquine-artesunate (MQ-AS) is recommended for chemoprophylactic treatment. It has a quick asexual blood-stage and gametocyte clearance rate (Adebayo et al., 2020). It is an effective schizonticidal drug and also inhibits heme polymerization (Adebayo et al., 2020). Studies regarding pyronaridine in artesunate-pyronaridine (AS-PYR) suggest it is

active against the erythrocytic stages of *Plasmodium*. It also targets all asexual stages of *P. falciparum* (Adebayo et al., 2020). It inhibits β-hematin formation which kills the parasite (Adebayo et al., 2020).

Table 3: ACT Characteristics Comparison

	Artemether-lumefantrine (AL)	**Artesunate-amodiaquine (ASAQ)**	**Artesunate - SP (AS-SP)**	**Artesunate - Mefloquine (AS-MQ)**	**Dihydro-artemisinin-piperaquine (DP)**	**Artesunate-pyronaridine (AS-PY)**
General comment	Most widely used ACT in Africa	Mostly used in West Africa, not recommend where SP-AQ used for SMC	Limited use (India, Middle East) due to SP resistance	Recommend for areas with multidrug resistance (SE Asia, South America)	Predominantly used in SE Asia	WHO note[130] clarifying AS-PYR considered safe and efficacious
Formulation	Fixed dose tablets and pediatric dispersible	Fixed dose tablets	Blister packed tablets, not fixed dose	Fixed dose tablets	Fixed dose tablets and pediatric dispersible	Fixed dose tablets and pediatric dispersible
Partner drug safety	Ample evidence from SE Asia, SSA	Ample evidence from SE Asia, SSA	Ample evidence from SE Asia, SSA	Ample evidence from SE Asia, increased risk of neuropsychiatric effects with repeated dosing	Ample evidence from SE Asia, SSA	Relatively limited evidence; acute, reversible liver enzyme increases
Partner drug half life, post treatment prophylaxis	4-6 days, limited to ~14-21 days	~4-10 days, limited to 21-28 days	~4-8 days, limited to 21-28 days	14-28 days, post treatment to 42+ days	14-28 days, post treatment to 42+ days, reduced risk of recurrent parasitemia and severe malaria vs. AL or ASAQ	14-18 days, mixed results on post-treatment prophylactic benefit over AL
Evidence of resistance to partner drug	No prior monotherapy, limited evidence	Some prior monotherapy, focal areas with evidence	Widespread resistance	Primarily in SE Asia	Evidence in SE Asia, no/limited evidence in SSA	Limited evidence in SE Asia, none in SSA
Partner drug molecular resistance locus[131]	*Pfmdr1* point mutations	*Pfmdr1* point mutations	*Dihydrofolate reductase (DHFR)* and *dihydropteroate synthase (DHPS)* point mutations	*Pfmdr1* copy number	*Plasmepsin 2* and *3* copy number, *Pfcrt* point mutations	Mechanism unknown

Note. "PMI Technical Guidance," 2024

This information is important because it shows the multitude of different compounds that can all be used for treatment of uncomplicated *P. falciparum*. ACTs are key for helping eliminate parasitemia in an individual and help keep the infection from turning severe. PMI's broad use of

drugs shows that PMI is aware that drug resistance is prevalent in SSA and may require a more tailored approach in areas where resistance has been caught. PMI's comprehensive approach to testing and treating malaria is reflective of their extensive knowledge of the biology of malaria and targets it on a cellular level to effectively treat and minimize the harms of malaria.

Threats to Current Initiatives

Although PMI does an excellent job evolving with new research and challenges, there are certain threats that pose a problem to its current goals. These threats highlight some key areas that need to be continually addressed and need to be changed as things evolve. Some of these threats also highlight some areas where PMI needs to become better and improve in certain areas to better address the situation at hand.

Resistance

It is important to have multiple drugs that target different mechanisms within the parasite because malaria has shown to be effective at becoming resistant. The majority of the antimalarial drug resistance arises from genetic mutations (Nosten & White, 2007). The reliance on ACTs as the main treatment for malaria shows how important it is to remain up to date on malarial resistance to these drugs. It also highlights the dangerous reliance PMI has fostered on the reliance of antimalarial drugs. Although ACTs remain one of the most vital resources to combat and treat malaria, there needs to be a push for alternatives. The introduction of the vaccine is key, but the research should not stop there. There needs to be continued support and push towards vaccinations for adults and ones that can help prevent malaria before it infects an individual.

Malarial parasites continue to show increasing resistance against some of the important insecticides used for prevention. Resistance to insecticides has been documented in all partner countries, showing its increasing importance to address ("17th Annual Report," 2023). Controlling the spread of malaria is proving an increasing issue because some of the leading preventative techniques are being evaded by the mutating parasite. This does raise concerns for the current mechanisms used to fight malaria and calls attention to why it is so critical to continue research and development on new tools. It is concerning to see that some of the main ways of combating malaria are becoming less effective and that malaria is becoming resistant. It requires a forward-thinking approach from PMI to ensure that proper detection and monitoring is conducted so they can stay ahead of it and prevent this from being a bigger issue.

One of the responses to this increasing rate of resistance is the movement away from standard pyrethroid nets, and adding additional chemicals. In 2022, more than 60% of the nets provided were newer with a combination of chemicals. This shows a quick response to the increasing rate of resistance. That being said, the parasite will continue to develop ways to evade new methods. PMI will need to maintain its detection capabilities and evolve with the parasite to keep up with the evolving parasite. The detection of resistant parasites shows that PMI's prevention tools and treatment must evolve with the changing parasite. As seen with ITNs, PMI is capable of introducing a new method and/or chemical to counter this resistance, but it is going to be an ongoing battle.

Deletions in P. falciparum Histidine-Rich Protein 2 and Protein 3 Genes

Most of the RDTs used detect the histidine-rich protein 2 (HRP2) which works in conjunction with HRP3 ("PMI Technical Guidance," 2024). Recent research has shown an increase in malaria parasites not producing the HRP2 and/or HRP3 antigens. The deletion of these protein genes means that there is an increased risk of a *P. falciparum* infection that goes by without detection. This is dangerous because without being able to accurately detect malaria infections, the transmission rate can increase, countering all the efforts PMI has worked hard for.

PMI is still determining the best course of action for detecting and monitoring these deletions, but are following the WHO risk assessment tool ("PMI Technical Guidance," 2024). This standardized protocol entails testing symptomatic patients with a HRP2 test and a non-HRP2 test like microscopy so then those with differing results can be assayed ("PMI Technical Guidance," 2024). Light microscopy allows for scientists to detect, quantify the parasitemia, and speciation, all vital for treating an infection ("PMI Technical Guidance," 2024). That being said, microscopy is dependent on the user, and it requires a well-trained individual to properly test with microscopy. While PMI does try to support researchers with training and monetary assistance, it has become a costly objective to maintain. PMI supported microscopy is usually only available at larger scale institutions like hospitals so it may be difficult to effectively monitor these deletions in more rural communities.

There are many challenges the fight against malaria is facing, and there isn't that much funding going into *hrp2/hrp3* deletions. Although this is a threat for PMI, it is not a leading priority. Researchers and partner countries need to be vigilant with testing and monitoring these deletions to ensure that the funding they receive is going as far as possible. Furthermore,

scientists and healthcare professionals need to be cognizant in alerting PMI and their country's healthcare institutions regarding deletions, so if it does start to exponentially increase, then these resources can make funding changes accordingly and respond quickly.

The Invasive Mosquito Anopheles stephensi

Although there has been progress on controlling and even eradicating malaria within the original four main strains of mosquitoes, the emergence of an invasive species of mosquito in Africa, *Anopheles stephensi*, is threatening all the progress made by PMI. This species is an efficient vector of malaria for both *P. falciparum* and *P. vivax* ("PMI Action Plan," 2023). This mosquito is dangerous and poses a serious threat to Africa because it breeds and thrives in both urban and rural environments.

PMI has predicted that as this species continues to spread, it puts an additional 126 million people at risk, a significant increase ("PMI Action Plan," 2023). This means that it requires more funding and attention along with continued efforts to better understand this strain. That being said, PMI has been very intentional with its strategy to continue its efforts with the other species, while also addressing the emerging issue with *Anopheles stephensi.* This has included changing their policy around larval source management and vector control strategies ("PMI Action Plan," 2023). PMI has also created a task force that focuses on this emerging issue to stay up to date and to continue to be flexible with the policy they are implementing.

Most mosquitoes lay eggs in natural habitats such as ponds, but *An. stephensi* lays its eggs in artificial water storage containers ("PMI Action Plan," 2023). That opens up the ability of mosquitoes to survive year round and no longer become dependent on rainfall. Many endemic

malaria areas have some relief during the dry season, when normal mosquitoes do not thrive, but this invasive species threatens that calm period and has caused unheard of outbreaks during these times. This threatens lots of the work PMI does and threatens the progress it has done in the partner countries.

One effective way to control *An. stephensi* is to add larvicide to the water where they often breed, larval source management (LSM). The larvicide used does not harm other local animals, is safe for human consumption, and for watering crops ("PMI Action Plan," 2023). Furthermore, it is a quick and efficient method to respond to *An. stephensi* within each country. PMI recognizes the threat that *An. stephensi* poses and creates an updated report on how to combat this species effectively. PMI's quick and comprehensive response to this threat shows how well-equipped this policy is to deal with emerging challenges.

This is all to say that PMI anticipates certain challenges and can respond swiftly and effectively to try and combat the threats they pose. This is a well structured policy because it provides enough structure to quickly respond to challenges through already established mechanisms, but also lends itself to some flexibility that can enable the policy to evolve with new threats. Figure 4 provides a more detailed approach to handling *An. stephensi* that addresses the biology of the mosquito while also coordinating with other infrastructures to ensure that the mosquito outbreak can be mitigated.

Figure 4: PMI recommended activities for combatting *An. stephensi*

		Scenario 1: ***An. stephensi*** **present**	**Scenario 2:** **At risk of invasion**
	**Surveillance**	• Conduct larval surveillance as part of any malaria outbreak investigation • Entomological monitoring (larval surveys, Prokopack aspiration) in high risk sites	• Training on *An. stephensi* identification • Investigate *Anopheles* that do not amplify in species ID PCR ○ Confirm positives with sequencing • Entomological surveys in ports and high risk sites
	**Vector Control**	• Implement appropriate *An. stephensi* vector control (i.e.- LSM)	• Plan and prepare for *An. stephensi* vector control by registering insecticides needed
	**Social Behavior Change**	• Determine appropriate SBC activities using PMI SBC guidance document linked here	
	**Multisectoral Coordination**	• Liaise with veterinary, population mobility, transport, commerce, agriculture, and education partners	• Plan for discussions with veterinary, population mobility, transport, commerce, agriculture, and education partners
	**Case Management**	• Ensure sufficient malaria commodities are present in areas with *An. stephensi*	• Plan and prepare for potential shifts in commodity needs if *An. stephensi* is detected
	**Community Health**	• Community-based entomological surveillance • Community-based larviciding • Field Epidemiology Training Program	• Community-based entomological surveillance • Plan and prepare for community-based larviciding • Field Epidemiology Training Program

Note. "PMI Action Plan," 2023

Climate Change

One of the major crises the world is facing is global climate change. This has dramatic repercussions including a significant impact on malaria. This is because malaria transmission is heavily dependent on temperature, rainfall, and humidity ("WHO Guidelines for Malaria," 2023). The warmer and wetter weather associated with climate change can create a perfect environment for malaria-carrying mosquitoes to breed and spread the disease. PMI predicts that due to the current climate trend, by 2030, the increased temperature and wetness from climate change can potentially put 22-36 million more people at risk for malaria exposure ("17th Annual Report,"

2023). Furthermore, severe weather is becoming more common and these storms can disrupt malaria programs that deliver lifesaving prevention tools and treatments.

PMI has already created some guidelines for addressing climate change. This includes making climate change data more accessible to partner countries so that they can combine these data and malaria patterns to determine the best time to use prevention tools. PMI is also finding ways to make certain tools such as temperature control for store rooms and tracking technology more dependent on solar power so if severe weather does occur, it is less likely to experience power outages ("17th Annual Report," 2023). This is important to maintain because lots of the drugs for treatments need to be temperature controlled and if weather disrupts that, lots of treatments may be ruined. When severe weather has hit areas and disrupted supply chains, PMI has rushed to support distribution of RDTs, ITNs, and treatments to those who are displaced ("17th Annual Report," 2023).

Not only is PMI ensuring that partner countries are equipped for climate change affecting malaria patterns and those exposed, but it is also pushing to make the infrastructure of the policy as green as possible. Between fiscal year 2019 to 2021, PMI decreased their supply chain greenhouse gas emissions by 50% and saved $28.7 million ("17th Annual Report," 2023). PMI also made transitions to sea and land freight instead of air to generate less emissions. They also improved packaging and loading to maximize efficiency and transportation ("17th Annual Report," 2023). Climate change is one of the biggest threats the world faces today, and is going to continue to leave lasting implications on many public health issues. It is going to be crucial in the next couple of years for PMI to remain vigilant in responding to the ways climate change affects PMI's partner countries. Everyone is going to need to be aware of ways to effectively

respond and provide solutions to ensure the protection and treatment of more people as climate change influences malaria transmission.

Future Health Crises

The COVID-19 pandemic halted the world and emphasized the increasing importance for global collaboration when dealing with public health crises. Malaria efforts were also significantly impacted by the pandemic and set PMI's efforts back. According to the 17th Annual Report to Congress reflecting on fiscal year 2022, an estimated 13.4 million malaria cases were attributed to the disruptions the pandemic caused on health services (2023).

That being said, PMI has used the COVID-19 pandemic as a way to be better prepared for another pandemic. This includes making sure that community health workers know how to properly test for diseases and also spreading awareness and information around. It also establishes a strong surveillance system that is equipped with analyzing data and responding in the best way based on the evidence. The key part is using the data retrieved from these analyses to lead the response. This highlights the reliance on data and research to influence the proper way to combat and respond to the disease. Having a policy already built on a biological basis sets a good precedent for future responses. It emphasizes the need for research and a true understanding of biology to help guide the efforts.

Furthermore, PMI has highlighted the importance of skilled lab techs and making supply chains more adaptable and resilient ("17th Annual Report," 2023). The combination of these two factors can help countries detect health crises quicker and more reliably. This then translates into an effective response where the supply chains for treatment and prevention methods can be

distributed. These factors all show that PMI is fully aware that it was lacking in preparedness for the COVID-19 pandemic and has changed its policy structure to meet these needs. That awareness demonstrates an adaptable mindset that puts on biology on the forefront of policy directions.

V. The Future of PMI and Future Foreign Health Policies

The United States President's Malaria Initiative is a long-lasting policy that continues to promote the elimination of malaria throughout the world. This disease still plagues many Sub-Saharan and Asian countries and needs to remain on the forefront of public health policy. The consistently high mortality rate and deaths per year raises questions as to whether or not PMI is making an effective impact within its partner countries. The goal of this paper is to analyze the biological aspects of the policy to see how it targets the disease on a cellular level. The rest of this paper is going to look at the future of this policy and its implications on future US foreign policy.

Room for Improvement

Although PMI does represent an excellent foreign policy through thoroughly researching and targeting the biology of malaria, there is always room for improvement. That is not a criticism of the entire policy, but instead is a way to provide some advances to bolster PMI’s efforts against malaria.

One area where there could be increased research and structure is surrounding sickle cell anemia. Heterozygous presentation of sickle cell anemia is prominent in SSA and provides some

interesting protective features against parasitemia. However, the homozygous sickle cell trait can also be harmful and dangerous to those with malaria. Sickle cell anemia offers an interesting perspective into the complexity of the two diseases and the way that the immune system responds to differing diseases. The current research surrounding sickle anemia and severe anemia suggest an increased need for future research into the relationship between sickle cell anemia and malaria. There needs to be more information regarding the specific mechanisms underlying the protective features of sickle cell anemia. Throughout PMI's policies and reports, there is minimal to no mention of sickle cell anemia, despite its high prevalence in its partner countries. PMI should recognize its significance in the future and that it may offer an important approach for improving public health. There may be potential interventions and preventive strategies that can come out of this research that may provide significant implications for malaria treatment.

Furthermore, PMI needs to continue to delve into the research surrounding malaria treatment and prevention with vaccines. The groundbreaking vaccine recommendation of RTS,S/AS01 was revolutionary in improving malaria-related childhood mortality. That being said, there needs to be a continued push for a vaccine that can be used for adults. In addition, multiple options must be provided to prevent parasite resistance to the vaccine and bolster an individual's protection from malaria. While PMI has been critical in the research and development of the malaria vaccine, they need to continue more research and development into other efficacious vaccines. Continued research is going to be crucial in the fight against malaria and providing a vaccine that is effective for all individuals.

Although there is a plateau in global funding against malaria, PMI cannot let that deter their efforts against the disease. There does need to be an increased push for gaining more funding to help aid their efforts. The US government is going to play an important role in

increasing funding for PMI, but it may not be reasonable to expect all the funding just from the US government. There may be a need to turn to different approaches for receiving funding, not just primarily from the US government. PMI has already fostered some private relationships with companies and organizations, but they may have to get creative and rely on funding from these outside sources more. In 2016, the British government and the Bill and Melinda Gates Foundation pledged an additional $4.3 billion to fight malaria ("£3 Billion Pledge," 2016). This shows that the global community is also heavily invested in the fight against malaria, but there needs to be a push for these groups to work together and rely on each other for resources and support to make that funding go the furthest it can. The stall in the increased funding for PMI suggests the need for the policy to get creative and rely on other countries and organizations as a way to bolster funding. That will be vital for making this money go the absolute furthest possible and fight malaria to their best abilities.

As mentioned above, the Bill and Melinda Gates Foundation may be a key resource for PMI to work with more closely. According to Melinda Gates, "Any goal short of eradicating malaria is accepting malaria, it is making peace with malaria" and for countries to only work on eliminating malaria in their own countries "is just unacceptable" ("Malaria - Eradication, Prevention," n.d.). Currently this foundation contributes around 5% of the annual investment for the fight against malaria. PMI and the Gates Foundation are not currently partners, but work with similar other groups with the same ultimate goal of eliminating malaria. The Gates Foundation also targets areas such as reaching those at risk, the importance and power of data, advancing innovation and research, and strengthening support ("Malaria - Eradication, Prevention," n.d.). These are all of similar interests to PMI, and making an official partnership between these two organizations could be in both of their best interests. PMI needs to continue to foster outside

relationships such as with the Gates Foundation to help increase funding and to share resources to improve the fight against malaria.

Conclusion and Future Implications

This paper aims to reveal the comprehensive mechanisms PMI employs to properly combat malaria at a cellular and biological level. It is absolutely critical to target this disease at that level because that is the only way that control and ultimately elimination will occur. While there are larger fixes that can be done to help control malaria, there is no better way to eliminate the disease than to inhibit the inner workings of it. PMI shows a flexible yet structured approach that draws from a multitude of different preventative and treatment options to all come together to lead the fight against malaria.

As shown throughout the paper, the use of preventative tools such as ITNs and IRS are critical for stopping the disease before a mosquito even bites. It helps target malaria using physical barriers and insecticides to decrease transmission rates. The range of insecticides used and the different mechanisms they target within the mosquito shows an extensive list of ways the PMI tries to combat malaria. It also shows the research and understating of resistance that PMI uses to guide selection and rotation. Furthermore, the exciting WHO recommendation for the use of the RTS,S/AS01 vaccine shows another prevention method that will likely play a key role in the upcoming years as a way to help protect children. The trials have shown a significant decrease in child mortality, a huge win for the fight against malaria. There needs to be further development into an effective vaccine for adults, but an approved vaccine for any group is a huge step in the right direction.

PMI is an excellent example of a US foreign policy that adapts to challenges while unwaveringly targeting the biology of malaria as its main focus. Throughout every avenue of its structure, PMI has found a way to relate it back to the cellular level of the disease to find a way to better combat it. Fighting malaria is an ongoing battle, but PMI reflects a comprehensive and effective policy that takes the biological mechanisms well into account to properly combat malaria and deserves to be used as a foundational tool for future US foreign public health policy. It uses physical blockades, a combination of insecticides and interventions, along with treatments all to target the disease from different angles. This allows for an overarching policy that successfully combats malaria on a biological level.

This research is important because as learned with the COVID-19 pandemic, proper and effective medical policies are vital now and into the future. PMI has established an excellent framework and understanding of malaria to successfully combat it by utilizing its biology to specifically target the mechanisms of the disease. PMI reflects a bipartisan supported policy that is constantly evolving and improving as new biological advancements are made. This policy shows the importance of a comprehensive framework that effectively targets the biological components of the disease while also establishing other mechanisms to have an overarching and successful policy.

PMI shows a forward-thinking approach to medical policy that can effectively target the disease on a cellular level while implementing structural and institutional changes at the same time. This impressive approach should be used as a foundation for future medical policy. It shows the importance of collaboration between countries while respecting and expecting independence and accountability within each country. PMI works in part because it instills

responsibility within each country but also provides the resources and support needed to bolster their individual healthcare system.

The U.S. President's Malaria Initiative sets a solid foundation for future US public health foreign policy. It is an impressive policy that addresses malaria from many angles, all targeting some aspect of the biology of the disease. It will be crucial for future policies to encompass a similar scope of biological mechanisms because that is going to lead the journey towards elimination. There will continue to be health crises that will require U.S. attention and public policies to aid other areas of the world. PMI has created an impressive, effective, and comprehensive framework for U.S. foreign public health policy that can and should be used for future policy campaigns to address urgent health crises.

References

£3 billion pledge to help end malaria deaths. (2016, January 25). GOV.UK. https://www.gov.uk/government/news/3-billion-pledge-to-help-end-malaria-deaths

Adebayo, J. O., Tijjani, H., Adegunloye, A. P., Ishola, A. A., Balogun, E. A., & Malomo, S. O. (2020). Enhancing the antimalarial activity of artesunate. *Parasitology research*, *119*(9), 2749–2764. https://doi.org/10.1007/s00436-020-06786-1

Centers for Disease Control and Prevention. (2020, July 16). *Biology of Malaria*. Centers for Disease Control and Prevention. https://www.cdc.gov/malaria/about/biology/index.html

Centers for Disease Control and Prevention. (2018, July 23). *Elimination of Malaria in the United States (1947-1951)*. Centers for Disease Control and Prevention. https://www.cdc.gov/malaria/about/history/elimination_us.html

Chrustek, A., Hołyńska-Iwan, I., Dziembowska, I., Bogusiewicz, J., Wróblewski, M., Cwynar, A., & Olszewska-Słonina, D. (2018). Current Research on the Safety of Pyrethroids Used as Insecticides. *Medicina (Kaunas, Lithuania)*, *54*(4), 61. https://doi.org/10.3390/medicina54040061

Crutcher JM, Hoffman SL. Malaria. In: Baron S, editor. Medical Microbiology. 4th edition. Galveston (TX): University of Texas Medical Branch at Galveston; 1996. Chapter 83.Available from: https://www.ncbi.nlm.nih.gov/books/NBK8584/

Cummings RD, Hokke CH, Haslam SM. Parasitic Infections. In: Varki A, Cummings RD, Esko JD, et al., editors. Essentials of Glycobiology [Internet]. 4th edition. Cold Spring Harbor

(NY): Cold Spring Harbor Laboratory Press; 2022. Chapter 43. Available from: https://www.ncbi.nlm.nih.gov/books/NBK579956/doi: 10.1101/glycobiology.4e.43

Dobbs, K. R., & Dent, A. E. (2016). Plasmodium malaria and antimalarial antibodies in the first year of life. *Parasitology*, *143*(2), 129–138. https://doi.org/10.1017/S0031182015001626

Empowering Angolan scientists to keep their country safe from malaria. U.S. President's Malaria Initiative. (2023, August 8). *https://www.pmi.gov/empowering-angolan-scientists-to-keep-their-country-safe-from-malaria/*

Empowering women in the fight against malaria: Blessing Ichekul leading the way in Nigeria. U.S. President's Malaria Initiative. (2024, January 30). https://www.pmi.gov/empowering-women-in-the-fight-against-malaria-blessing-ichekul-leading-the-way-in-nigeria/

Fact sheet about malaria. World Health Organization. (2023, December 4). https://www.who.int/news-room/fact-sheets/detail/malaria

Grimwade, K., Swingler, & G (2003). Cotrimoxazole prophylaxis for opportunistic infections in adults with HIV. *The Cochrane database of systematic reviews*, *2003*(3), CD003108. https://doi.org/10.1002/14651858.CD003108

Hafalla, J. C., Silvie, O., & Matuschewski, K. (2011). Cell biology and immunology of malaria. *Immunological reviews*, *240*(1), 297–316. https://doi.org/10.1111/j.1600-065X.2010.00988.x

Henrici, R. C., Sautter, C. L., Bond, C., Opoka, R. O., Namazzi, R., Datta, D., Ware, R. E., Conroy, A. L., & John, C. C. (2021). Decreased parasite burden and altered host response in children with sickle cell anemia and severe anemia with malaria. *Blood Advances*, *5*(22), 4710–4720. https://doi.org/10.1182/bloodadvances.2021004704

Hong S. C. (2007). The Burden of Early Exposure to Malaria in the United States, 1850-1860: Malnutrition and Immune Disorders. *The journal of economic history*, *67*(4), 1001–1035. https://doi.org/10.1017/S0022050707000472

Hyde J. E. (2005). Exploring the folate pathway in Plasmodium falciparum. *Acta tropica*, *94*(3), 191–206. https://doi.org/10.1016/j.actatropica.2005.04.002

An Invasive Mosquito Threatens the Progress to End Malaria in Africa. U.S. President's Malaria Initiative. (2022, October 26). https://www.pmi.gov/an-invasive-mosquito-threatens-the-progress-to-end-malaria-in-africa

Jamet, H. (2022, August 18). *Why the interceptor G2 net could be a game changer for malaria eradication*. Bill & Melinda Gates Foundation. https://www.gatesfoundation.org/ideas/articles/ig2-nets-malaria-eradication-financed-by-the-global-fund

Kovacs, S. D., Rijken, M. J., & Stergachis, A. (2015). Treating severe malaria in pregnancy: a review of the evidence. *Drug safety*, *38*(2), 165–181. https://doi.org/10.1007/s40264-014-0261-9

Laurens M. B. (2020). RTS,S/AS01 vaccine (Mosquirix™): an overview. *Human vaccines & immunotherapeutics*, *16*(3), 480–489. https://doi.org/10.1080/21645515.2019.1669415

Luzzatto L. (2012). Sickle cell anemia and malaria. *Mediterranean journal of hematology and infectious diseases*, *4*(1), e2012065. https://doi.org/10.4084/MJHID.2012.065

Malaria - Eradication, Prevention, Through Innovation & Data. Bill & Melinda Gates Foundation. (n.d.). https://www.gatesfoundation.org/our-work/programs/global-health/malaria

Malaria in Africa. UNICEF Data. (2024, January 11). https://data.unicef.org/topic/child-health/malaria/

Metz J. (2007). Folic acid metabolism and malaria. *Food and nutrition bulletin*, *28*(4 Suppl), S540–S549. https://doi.org/10.1177/15648265070284S407

Miller, L. H., Ackerman, H. C., Su, X., & Wellems, T. E. (2013). Malaria biology and disease pathogenesis: Insights for new treatments. *Nature Medicine*, *19*(2), 156–167. https://doi.org/10.1038/nm.3073

New frontiers in vector control. World Health Organization. (2022, April 11). https://www.who.int/news-room/feature-stories/detail/new-frontiers-in-vector-control

Nosten, F., & White, N. J. (2007). Artemisinin-Based Combination Treatment of Falciparum Malaria. *The American Journal of Tropical Medicine and Hygiene*, *77*(Progress and Perspectives), 181–192. https://doi.org/10.4269/ajtmh.2007.77.181

Oxborough, R. M., N'Guessan, R., Jones, R., Kitau, J., Ngufor, C., Malone, D., Mosha, F. W., & Rowland, M. W. (2015). The activity of the pyrrole insecticide chlorfenapyr in mosquito bioassay: Towards a more rational testing and screening of non-neurotoxic insecticides for malaria vector control. *Malaria Journal*, *14*(1). https://doi.org/10.1186/s12936-015-0639-x

Schumacher, R. F., & Spinelli, E. (2012). Malaria in children. Mediterranean journal of hematology and infectious diseases, 4(1), e2012073. https://doi.org/10.4084/MJHID.2012.073

A Scientist behind vital research on malaria vaccines: Q&A. (2024, February 28). https://www.pmi.gov/a-scientist-behind-vital-research-on-malaria-vaccines-qa/

Stover, K. R., King, S. T., & Robinson, J. (2012). Artemether-Lumefantrine: An option for malaria. *Annals of Pharmacotherapy*, *46*(4), 567–577. https://doi.org/10.1345/aph.1q539

About us. U.S. President's Malaria Initiative. (n.d.). https://www.pmi.gov/about-us/

What we do. U.S. President's Malaria Initiative. (n.d.). https://www.pmi.gov/what-we-do/

Where we work. U.S. President's Malaria Initiative. (n.d.). https://www.pmi.gov/where-we-work/

White, M. T., Verity, R., Griffin, J. T., Asante, K. P., Owusu-Agyei, S., Greenwood, B., Drakeley, C., Gesase, S., Lusingu, J., Ansong, D., Adjei, S., Agbenyega, T., Ogutu, B., Otieno, L., Otieno, W., Agnandji, S. T., Lell, B., Kremsner, P., Hoffman, I., Martinson, F., … Ghani, A. C. (2015). Immunogenicity of the RTS,S/AS01 malaria vaccine and implications for duration of vaccine efficacy: secondary analysis of data from a phase 3 randomized

controlled trial. *The Lancet. Infectious diseases*, *15*(12), 1450–1458. https://doi.org/10.1016/S1473-3099(15)00239-X

World Health Organization. (2023). *Seasonal malaria chemoprevention with sulfadoxine-pyrimethamine plus amodiaquine in children: a field guide*. https://iris.who.int/bitstream/handle/10665/368123/9789240073692-eng.pdf?sequence=1

World Health Organization. (2024, October 16). *WHO guidelines for malaria.* https://iris.who.int/bitstream/handle/10665/373339/WHO-UCN-GMP-2023.01-Rev.1-eng.pdf?sequence=1

World Health Organization. (November 2023). *The RTS,S Malaria Vaccine.* https://cdn.who.int/media/docs/default-source/immunization/mvip/who_mvi_infographic-jan2024-01_approved.pdf?sfvrsn=43d3653a_2&download=true

USAID. (January 2017). *Integrated vector management programs for malaria vector control (version 2017).* https://d1u4sg1s9ptc4z.cloudfront.net/uploads/2021/03/integrated-vector-management-programs-for-malaria-vector-control-programmatic-environmental-assessment-2017-2.pdf

U.S. President's Malaria Initiative. (April 2023). *17th Annual report to congress.* https://d1u4sg1s9ptc4z.cloudfront.net/uploads/2023/05/USAID_PMI_2022_Report_to_Congress.pdf

U.S. President's Malaria Initiative. (2021, October 6). *End Malaria Faster*. https://d1u4sg1s9ptc4z.cloudfront.net/uploads/2021/10/10.04Final_USAID_PMI_Report_50851.pdf

U.S. President's Malaria Initiative. (2023, January 30). *PMI action plan to respond to the threat of Anopheles stephensi in Africa.* https://d1u4sg1s9ptc4z.cloudfront.net/uploads/2023/03/PMI-action-plan-for-Anopheles-stephensi.pdf

U.S. President's Malaria Initiative. (2024). *PMI technical guidance: FY 2024.* https://d1u4sg1s9ptc4z.cloudfront.net/uploads/2023/02/PMI-FY-2024-Technical-Guidance.pdf