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UNIVERSITY OF MICHIGAN ROSS SCHOOL OF BUSINESS

Strategic and Economical Solutions for the Eradication of Malaria

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Executive Summary

Malaria is an enormous global health issue that kills about one million annually. It is a parasitic disease spread between hosts (humans) by vectors (mosquitoes). If any part of this cycles is eliminated (i.e. mosquitoes can bite humans or no humans have the disease), then malaria will be eradicated. In spite of malaria being eradicatable for the last half century, it continues to ravage multiple continents. This study evaluates the global efforts in malaria prevention and proposes an optimal strategic and economical solution to fix the growing malaria epidemic.

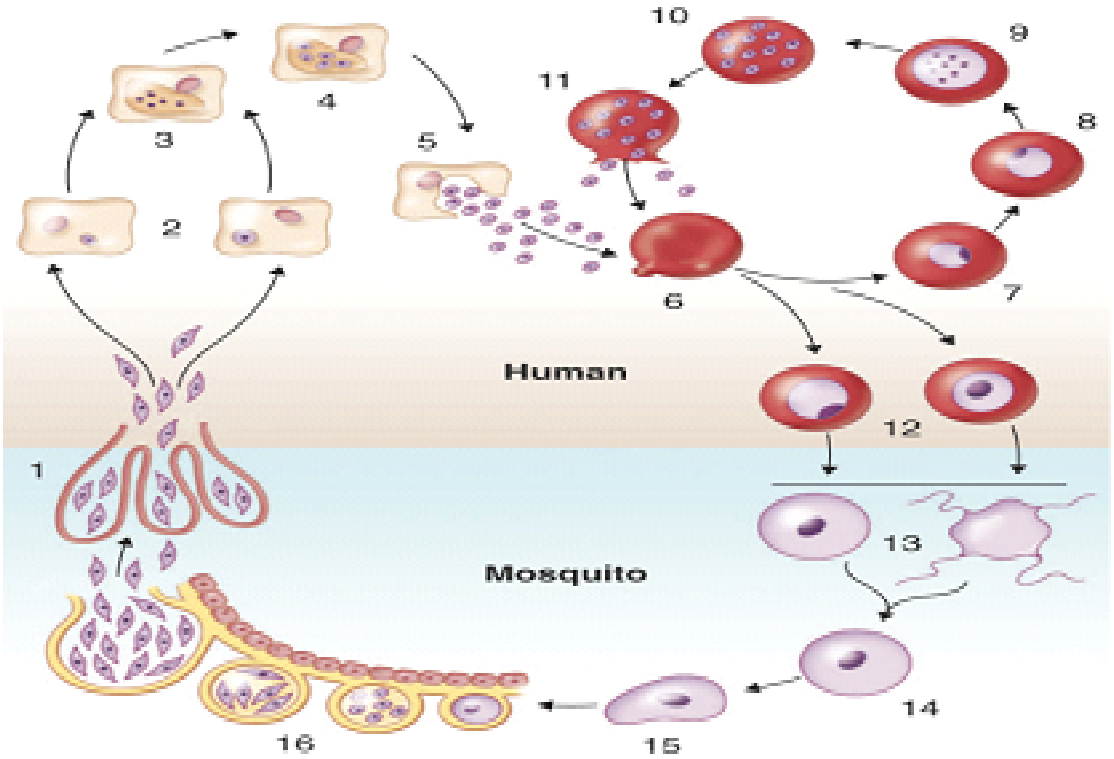
Pathophysiology of malaria

Malaria is characterized by recurrent fever and chills, which are caused by the coordinated breaking of red blood cells infected by the *Plasmodium* parasite. The severity of infection is determined by the concentration of parasites in the blood, which species of *Plasmodium* is involved, the amount of red blood cell ruptured, and the amount of inflammatory mediators (cytokines) that the body releases as a result of red blood cell rupture (Krogstad). Although there are four *Plasmodia* species which cause malaria, most deaths occur in children younger than 5 years old, who live in sub-Saharan Africa, who are infected by the sub-species *Plasmodium falciparum* (Krogstad).

Most patients make a complete recovery after treatment with antibiotics, and almost all cases are 100% treatable. A small percentage of patients require more invasive treatment with intravenous fluids for hypoglycemia, dialysis for renal failure, or heart monitoring for arrhythmias as a side effect of the antibiotic.

Although some individuals who are continually re-infected show decreased severity of disease over time, humans cannot gain immunity to malaria (Krogstad). Both immunity to malaria and a vaccine against malaria are difficult to mount as malaria is a genetically variable, parasitic disease (antigenic variability) that has four separate life cycles within the human blood stream (**Figure 1**). Malaria also has genes (*var* genes) that allow it to label red blood cells in a way that evades the immune system (Krogstad).

Figure 1: Malaria Life cycle within the human blood stream



Sporozoites from the salivary gland of a female *Anopheles* mosquito are injected under the skin (1). They then travel through the blood stream to the liver (2) and mature within hepatocytes to become tissue schizonts (4). Up to 30,000 parasites are then released into the blood stream as merozoites (5) and produce symptomatic infection as they invade and destroy red blood cells. However, some parasites remain dormant in the liver as hypnozoites (2, between 1 and 3). They are the parasites that cause relapsing malaria (in *Plasmodium vivax* or *Plasmodium ovale* infection). Once within the blood stream, merozoites (5) invade red blood cells (6) and mature to the ring (7, 8), trophozoite (9), and schizont (10) asexual stages. Schizonts lyse their host red blood cells as they mature and release the next generation of merozoites (11), which invade previously uninfected red blood cells. Within the red blood cell, some parasites differentiate to sexual forms (male and female gametocytes) (12). When taken up by a female *Anopheles* mosquito, the gametocytes mature to male and female gametes, which produce zygotes (14). The zygote invades the gut of the mosquito (15) and develops into an oocyst (16). Mature oocysts produce sporozoites, which migrate to the salivary gland of the mosquito (1) and repeat the cycle. The horizontal line between 12 and 13 indicates that absence of the mosquito vector prevents natural transmission by means of this cycle. Infection by the injection of contaminated blood bypasses this constraint and permits transmission among intravenous drug addicts or to recipients of blood transfusions. *(From Krogstad DJ: Blood and tissue protozoa. In Schlechter M, Medoff G, Eisenstein BI [eds]: Mechanisms of Microbial Diseases, 2nd ed. Baltimore, Williams & Wilkins, 1993, p 600.)*

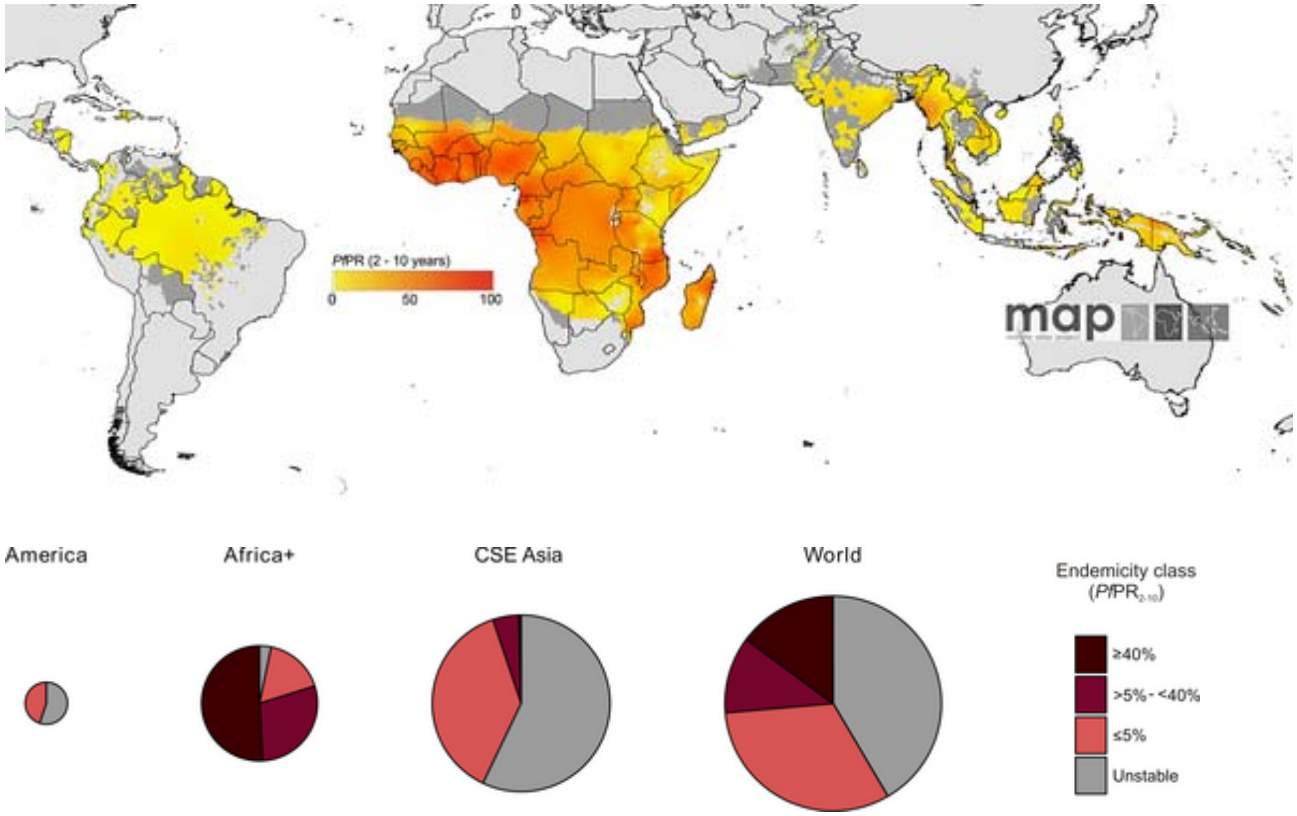
Prevalence and distribution

Malaria is one of the most common diseases worldwide, with over a half billion cases per year resulting in about a million deaths per year (Krogstad). Globally, 1.38 billion people are at risk for malaria (Hay). Of these, 0.69 billion are found in Central and South East Asia (CSEA), 0.66 billion in Africa, Yemen, and Saudi Arabia (Africa), and 0.04 billion in the Americas (Hay).

Hay, et al was the first in 40 years to calculate the endemicity of malaria across the globe. What Hay et al found was that those living in the Americas have a ≤ 5% risk of becoming infected within 10 years. In CSEA, 88% of those have ≤ 5% risk, 11% have an intermediate risk between 5 and 40%, and 1% have high risk of ≥ 40% of becoming infected within 10 years. In the Africa, 0.35 billion people have ≥ 40% risk of

becoming infected within 10 years, with 0.20 billion having between 5% and 40% risk and 0.11 billion have ≤ 5% risk of becoming infected within 10 years (Hay). The endemicity and population weighted risk of malarial infection can be seen in **Figure 2** (Hay).

Figure 2: Worldwide malaria endemicity (Hay)



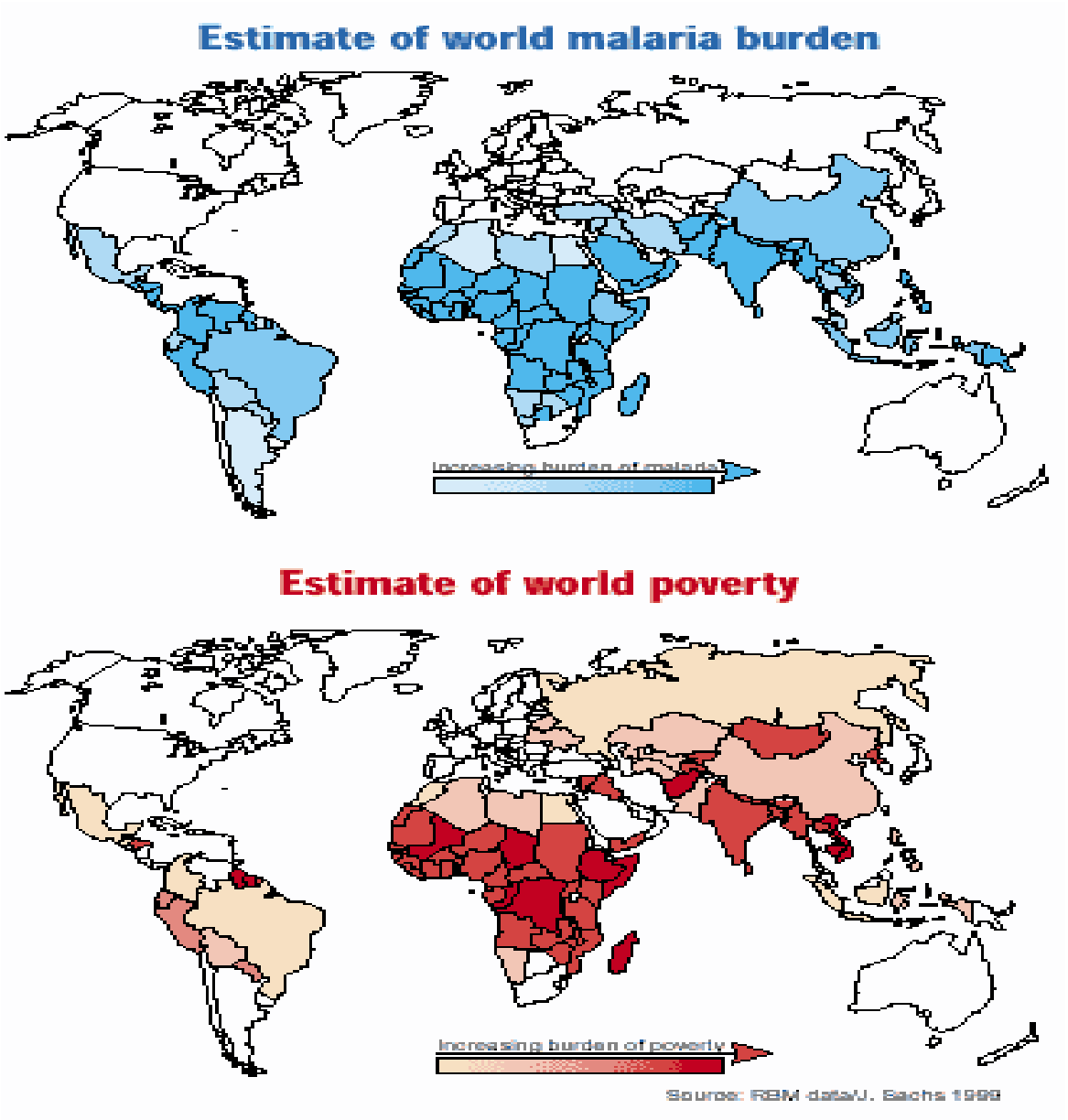
Of the 1.38 billion people at risk of stable P. falciparum malaria, 0.69 billion were found in Central and South East Asia (CSE Asia), 0.66 billion in Africa, Yemen, and Saudi Arabia (Africa+), and 0.04 billion in the Americas. All those exposed to stable risk in the Americas were in the lowest endemicity class ($PfPR_{2-10}$ ≤ 5%). The vast majority (88%) of those living under stable risk in CSE Asia were also in this low endemicity class; a small remainder (11%) were in the intermediate endemicity class ($PfPR_{2-10}$ > 5 to < 40%); and the remaining fraction (1%) in high endemicity ($PfPR_{2-10}$ ≥ 40%) areas. High endemicity was widespread in the Africa+ region, where 0.35 billion people are at this level of risk. Most of the rest live at intermediate risk (0.20 billion), with a smaller number (0.11 billion) at low stable risk (Hay).

By developing the first endemicity map in four decades, Hay et al. has allowed organizations a means by which to efficiently allocate preventative resources and analyze progress. Although prevention is possible with the current technology, Africa's high endemicity and population would make this extremely capital intensive. Because of the multiplication effects of the much larger CSEA population, malaria poses a huge public health threat there, but its huge population makes eradication with current technologies prohibitively expensive. The lower endemicity and population of the Americas and Europe make eradication a real possibility with current technologies (Hay).

Economic impact of malaria

The macro-economic impact of malaria is staggering. Annual economic growth and prosperity in endemic malaria countries is historically lower than in countries without malaria. Economists believe that malaria is responsible for a GDP 'growth penalty' of up to 1.3% per year in some African countries (RBM). **Figure 3** shows the staggering correlation between endemic malarial countries and world poverty.

Figure 3: Economic Burden of Malaria (RBM)



In endemic countries, a higher than average proportion of per person expenditure is targeted towards malaria treatment or prevention in the form of insecticide treated mosquito nets (ITNs), doctors' fees, anti-malarial drugs, transport to health facilities, and support for the patient during hospital stays (RBM). A disproportionate amount of public expenditures are also spent on malaria, which include maintaining health facilities and health care infrastructure, publicly managed vector control, education and research. In some countries with a heavy malaria burden, the disease may account for as much as 40% of public health expenditure, 30-50% of inpatient admissions, and up to 50% of outpatient visits (RBM).

Countries must begin seeing malaria prevention as an investment in economic prosperity and poverty reduction, not as a cost. A heavy disease burden is proven to directly and indirectly strip countries of prosperity and capital. Macro-economically, global leaders should do their part to cut tariffs on all preventative technologies (nets, insecticides, etc…). From a regulatory standpoint, countries should also take steps to regulate the quality of preventative strategies, assuring that any and all private funds are spent on proven products.

Prevention/Eradication Strategies

Malaria prevention/eradication should be a global priority because malaria has a devastating human and economic impact and because we have the technology to eradicate it. Malaria is a parasitic disease that is spread between hosts (humans) by vectors (mosquitoes). Thus, if any part of this cycles can be eliminated (i.e. mosquitoes can bite humans or no humans have the disease), then malaria will be completely eradicated. Because malaria is a lifelong disease if left untreated, and because young children and pregnant mothers suffer the highest mortality, prevention in pregnant women and young children is a priority.

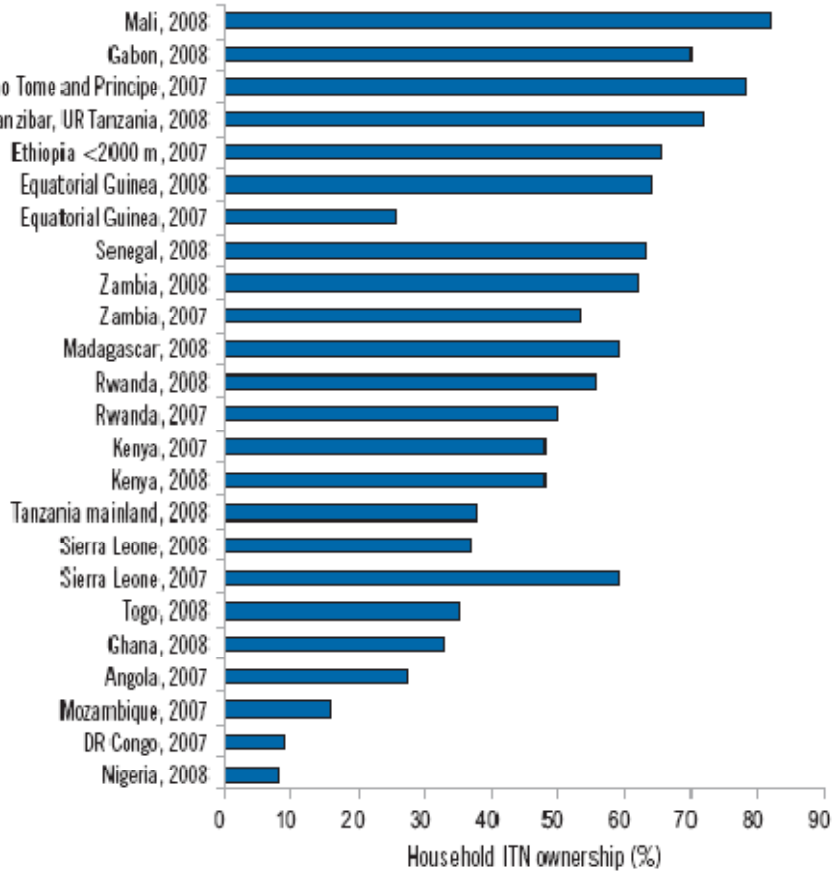
There are four main preventative/eradication strategies, three current and one future candidate. These strategies are outlined below and include long-lasting insecticide treated nets, indoor residual insecticide spraying, antimalarial drug treatment, and malaria vaccines:

- Long-lasting insecticide treated nets (LLINs): Mosquito nets are needed to protect individuals from mosquito bites/malarial infection while they sleep. If these nets are treated with insecticides, they are shown to repel mosquitoes better than if they are not impregnated with insecticides. Long-lasting nets are those considered to have a usable life greater than three years. A long lasting net is important because the longer lasting the net, the fewer consumer "touches" distributers need to make. Adequate distribution has been a limiting factor in net disbursement.

  The WHO has found that highly subsidized or free nets provided to mothers at free anti-natal healthcare visits are the most effective and efficient way of net distribution. Approximately 140 million LLINs were delivered to high-burden countries in African between 2006–2008 (WHO). Assuming a three year life span, 336 million need to be delivered annually. Unfortunately, delivery numbers are 25% higher than the disbursed number of nets, making the shortfall even more staggering (WHO). Estimates show that only 31% of African households own at least one

ITN, and only 24% of children under 5 years of age had used an ITN in 2008 (WHO). Net ownership is below 10% in the Congo and Nigeria, two very populous countries (WHO). Household penetration of LLINs by African country can be seen in **Figure 4**:

Figure 4: Household insecticide treated net penetration by African countries (WHO)



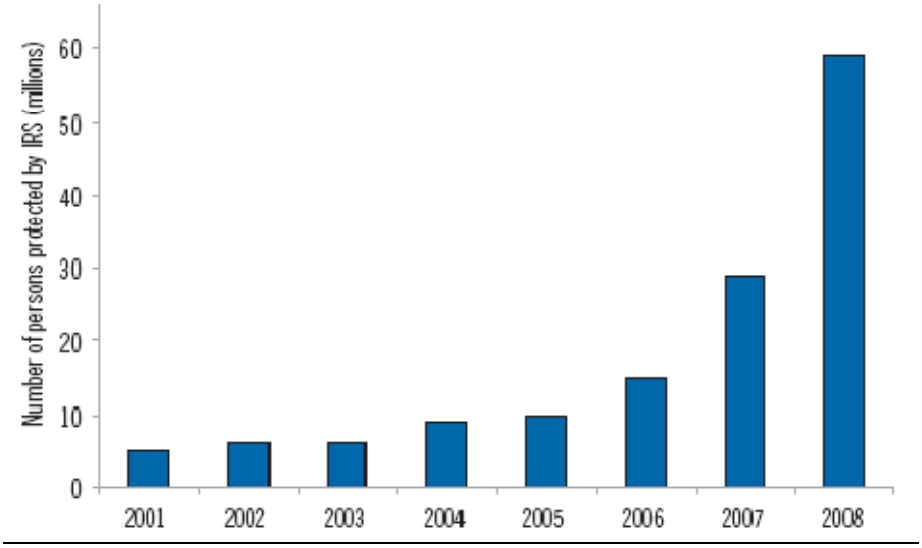
Although penetrations in countries such as Mali or Gabon seem impressive, one must remember that more than one net is needed per household as the average African household has 5.6 members (UN). If a mosquito bites a malaria infected person in the next bed, and then bites an un-netted person next door, or in the next room, malaria will still be spread. Thus a statistic such as *households with all members sleeping under nets*, or *communities with 100% net coverage* would be a more insightful and useful statistic as it would be in line with how malaria is spread and how it needs to be prevented. For LLINs to be effective in the fight to eradicate malaria, two conditions must be met:

1. All individuals must sleep under an LLIN.
2. Entire communities must have near 100% penetration and usage of LLINs to eliminate the human reservoir.

- <u>Indoor residual insecticide spraying (IRS):</u> IRS is a very important aspect of malarial control as it kills residual mosquitoes living in houses (where they most often rest after taking a blood meal)

and repels mosquitoes from entering houses. The use of a long-lasting insecticide and repellent is important in malaria prevention, as it reduces the number of sprayings required by increasing the interval between sprayings. DDT is the preferred agent as it is cost effective and has a residual effective for 6 months. Trends in IRS penetration can be seen in **Figure 5**.

Figure 5: Households treated by at least one round of IRS (WHO)



By 2008, 59 million in Africa were protected by IRS, but this still represents only 9% of the high risk population (WHO). Using IRS for prevention has three main weaknesses:

1. Mosquitoes are becoming immune to DDT.
2. For IRS to be effective, strict protocols and usage procedures must be followed. Most countries do not have the infrastructure or capacity to provide training, oversight, and monitoring (WHO).
3. IRS needs to be performed in over 80% of houses, barns, sheds, and outbuildings (WHO) within a community or a 2-4 square km area for effective malaria prevention (Ulrike Fillinger).

For an IRS strategy to be effective, two conditions must be met:

1. Buy in from the government within which it will be used. The government will have to provide the authority to regulate IRS usage.
2. The program will have to be rolled out on a community by community basis, ensuring >80% penetration within each community.

Until a community has >80% penetration, LLINs and IRS will have to be used in conjunction, which would effectively waste any funds spent on IRS. IRS needs high penetration or it offers little preventative benefit.

- Antimalarial drug treatment: Uncomplicated malaria (*Plasmodium falciparum*) is treated with artemisisin-based combination therapy (ACT). More complicated malaria and resistant malaria

(*Plasmodium vivax*) is treated with longer courses of multiple drugs (WHO). Because humans are the reservoir for malaria, any human who has malaria and is not treated could be bitten and spread malaria to another human by the mosquito that bit that original carrier. To eliminate malaria, the human reservoir needs to be eliminated via effective treatment. There are three main obstacles to universal and effective treatment:

1. Rare, but serious hemolysis as a result of the hereditary African G-6-PD trait.
2. Higher rates of individuals not completing treatment due to the long and more complicated courses of antibiotics (14 days with for resistant malaria).
3. Evolving resistance of Plasmodium to the current drugs. This is accelerated by individuals not taking the full courses of antibiotics.

Two new development opportunities would optimize malaria treatment and eliminate the human reservoir:

1. A simple, economical, at home malaria test that allows any individual to test themselves for malaria any time they or anyone in their family becomes febrile.
2. Development of an economical, single dose, depot treatment that allows easy, complete, "one touch" treatment.

Rapid recognition of a malaria infection, followed by rapid, simple, safe, economical, and complete treatment will be the only way to eliminate the human reservoir.

- Malaria vaccine: Just as with polio or any other epidemic disease, the successful role out of a malaria vaccine would be the ultimate tool and provide the most important step towards the eradication of malaria. The Gates Foundation views a malaria vaccine as a priority and has donated $10 billion to HIV and malaria vaccine research (Lancet). High hopes are pinned on a vaccine because of the pre-existence of vaccine rollout infrastructure in Africa and Asia (the two places where endemicity and/or high population make current strategies ineffective and prohibitively expensive). In some developing countries, there is almost 90% coverage by immunizations, so a malaria vaccine would join an existing and proven infrastructure/delivery system (Brown). With bed nets there is no existing infrastructure/delivery system, so every country is trying to act independently and costs of infrastructure development are high (Brown).

  Ten years ago, a malaria vaccine was thought to be impossible, but in 2006 at the Global Vaccine Research Forum, the Vaccine Technology Roadmap was developed as a way to organize and accelerate malaria vaccine development (Brown). Three main reasons make a vaccine against malaria difficult to produce and roll out:

  1. Malaria is a genetically variable, parasitic disease (antigenic variability) that has four separate life cycles within the human blood stream.
  2. Malaria has genes (*var* genes) that allow it to label red blood cells in a way that enables them to evade the immune system (Krogstad). Malaria has been a successful human parasite because it does not illicit a strong immune response. Generally, diseases that

do not illicit strong immune responses are poor candidates for vaccines as the strong immune response is what allows your immune system to "remember" the disease.

3. Cost is a huge barrier for any vaccine roll out. Current vaccines, such as the pneumococcal vaccine, could provide massive mortality benefits, as pneumonia is one of the top three killers of children in world, but countries and people cannot afford the vaccine.

Leading the way to an age of malaria vaccines is GlaxoSmithKline's RTS S/AS malaria vaccine. Currently, this vaccine is entering phase III trials. Trials show it has reduced malaria episodes by 53% in children aged 5–17 months, and in 65% of infants (aged less than 12 months), and it has a favorable safety profile (Morris). This is an improvement from the previous vaccine which only offered 30-40% protection (Morris). Although current vaccines show promise, for a vaccine to be move us towards malaria eradication, three main conditions must be met:

1. It must be highly effective (>80%) in preventing malaria and its effect must be long lasting and not require multiple booster immunizations.
2. It must me affordable or highly subsidized or free.
3. It must be universally available via the already proven vaccine infrastructure.

Current WHO Strategy for Malaria Eradication/Prevention

The WHO dedicates an entire section of their ninety-page 2009 World Malaria Report to their strategy (attached in Appendix). Unfortunately, their strategy section only includes eradication goals, preferred treatment recommendations, and funding requirements/shortfalls. A strategy is a method by which to reach goals. Although it is good to have goals, treatment recommendations, and recognize funding shortfalls, these do not comprise a strategy. They are goals. After reading the complete 2009 World Malaria Report, a comprehensive strategy is not found. But three common themes are evident:

1. The WHO breaks down the world into six sectors, African, Americas, South-east Asia, Europe, eastern Mediterranean, and Pacific.
2. If the WHO wishes to eradicate malaria with its current technology and methods, about five billion dollars per year would be needed (~$5 per person). Currently, the WHO receives about $650 million, 80% of which is used in Africa.
3. Eradication of malaria as soon as possible – this is measured on a country by country basis and not quantitatively analyzed for regional progress or what regional progress should be.

Numerous issues exist with the WHO's malaria eradication strategy (or lack thereof), yet five are glaring:

1. The WHO has not communicated a strategy.
2. The WHO's overarching measure of success is eradication progress on a country by country basis, which is not aligned with methods that will produce long-lasting eradication. To eradicate malaria, entire regions need to be cleared of disease to prevent frequent reintroduction across borders. Thus, saying you are making progress in a few small, non-populous countries sounds nice, but is relatively meaningless in the global fight to eradicate malaria.
3. Currently, Africa has less than half of the world's population that is at risk for malaria. Yet Africa receives 80% of the funding. Within Africa, the WHO is providing the most intensive efforts in

small, non-populous countries. Eliminating malaria in a small non-populous country surrounded by populous, high endemicity countries will lead to high malarial reintroduction pressure. Additionally, targeting these smaller, interspersed countries will not allow synergies to be gained as time progresses. Because eradicated states will not share borders under the current strategy, you provide fewer buffers against reintroduction and need to protect a smaller relative area with a relatively longer border. Simple geometry prove this to be a terrible strategy.

4. The WHO has not properly laid out strong treatment recommendations. By not firmly implementing proper controls over treatment regiments, resistance to ACTs, some of the most cost effective treatments, has increased and compromised their effectiveness.
5. The WHO is implementing a $5 billion strategy of with $650 million. The WHO communicates no strategy on how to increase funding to levels needed to implement their strategy or how they are going to adjust their strategy since they have ~10% of the funding needed to implement their current strategy.

What is the Best Malaria Eradication Strategy?

An optimal strategy to eradicate should have no agenda besides the most efficient, realistic, and practical way to eradicate malaria. Concern for what is "in vogue" should have no bearing on the best lifesaving strategy. An optimal strategy addresses the current problem, with the current resources, and the current technologies. The short term strategy should also include actions that optimize controllable factors in the present to maximize one's ability to succeed at reaching long term goals in what is predicted to be the most likely future scenario.

When looking at helping any population that is suffering from disease, it is important to look at more than the numbers and to keep in mind that real human lives and suffering will be impacted by the recommendation and decisions made. In Asia, in Africa, and in South America, a human life carries the same value. The overarching principles of an optimal malaria eradication strategy are the following:

- Target individuals who will have the greatest impact per life by elevating those peoples' quality of life in the greatest way per person.
- Produce the greatest sustained effect with the current technologies and funding. Not creating sustained effects is a waste of precious capital.
- Provide proper investment in future technologies in the hopes of providing greater sustainability that is more cost effective.

Clearly, the WHO's fight against malaria has made progress in some areas of Africa (Wakabi), and as the world recognized health authority, the WHO is a necessity in any suggested strategy (Senior). Any strategy to eradicate malaria needs to act through the WHO. The problem is not the WHO, it is the WHO's strategy.

The suggested malaria eradication strategy to produce the greatest, most sustainable, and most significant impact will act through six main pillars:

- **A regional approach:** For malaria to be eradicated the human infection pool must be eliminated and the transmission via mosquitoes must be prevented. Reintroduction via infected

mosquitoes or humans crossing boarders must be eliminated for an eradication strategy to have sustained effects. Because of this, eradication must be implemented within an entire region, to prevent individuals or mosquitoes that frequently travel across borders or mosquito larvae that can float down rivers or across lakes from continually re-infecting a country. The current strategy that makes progress in small, non-populous countries that are surrounded by large, high endemicity countries is nonsensical and does not produce sustainable results. By eliminating malaria on a regional basis, traction in malaria elimination can be gained, which allows for cost, treatment, and implementation synergies to be gained. This will lead to decreased annual funds needed for eradication in the targeted region(s). Currently, there are not enough funds to implement a regional plan eradication malaria for the 0.66 billion people in Africa or the 0.69 billion people in Asia.

- **~100% coverage on a community by community basis:** An average mosquito ranges over approximately 2-4 square kilometers and bites multiple individuals over the course of its life (Ulrike Fillinger). Therefore, to prevent the spread of malaria, it is essential to protect all those within the home range of infected mosquitoes, prioritizing the highest endemicity areas. By not doing so you are sitting on a proverbial time bomb, because all it takes is one infected person traveling through a village or one infected mosquito wandering into a town to re-infect the entire community. Near 100% prevention and treatment penetration is essential, not optional.
- **Use of improved LLINs, IRS, larvicide, and repellents (where applicable):** Over-reliance on any one drug or one prevention strategy increases the likelihood of resistance and threatens the future efficacy of malaria control (Ulrike Fillinger). Therefore, the suggested strategy increases the likelihood of current and sustainable success by integrating LLINs, IRS, and larvicide in the following ways:
    - Improved LLINs (long lasting insecticidal nets): Untreated nets offer little protection (Gerry F. Killeen). Current LLINs do a good job at protecting individuals, but some improvements to the product and to distribution should be made. An LLIN's protective factor would be greatly enhanced if it also had incorporated repellant characteristics (Gerry F. Killeen). Additionally, nets need to be pre-treated. By pre-treating the nets, rather than having users treat them, proper usage increases from 22% to 52% (Marchant). The optimal distribution strategy combines private and public sector ventures, which combine the effectiveness and efficiency of private ventures with the capital of the public sector (Gerry F. Killeen). Additionally, nets must be highly subsidized and/or free. Without near free nets, the lowest socio-economic classes will not receive or seek out nets (Marchant).
    - IRS (indoor residual spraying): Using IRS alone is not optimal. But by using IRS, with >80% coverage of buildings within a 2-4 square kilometer area with a cheap and effective agent such DDT provides a significant benefit. When IRS is used with LLINs, the benefit is additive. There is an 80% reduction in episodes of *P. vivax* when treated nets and IRS are used rather than nets alone (N Hill).
    - Larviciding: Although this approach has dropped out of vogue in recent times, it shows great promise in areas where standing water in the form of ponds or lakes are easily identifiable. Recent, controlled studies show huge benefits from larviciding. Larviciding

was associated with an additional 85.9% reduction in adult mosquitoes resting indoors (Ulrike Fillinger). This reduction in indoor mosquitoes translated into fewer bites and less malaria transmission. At baseline and individual gets 10–12 infectious bites per person per night. While using nets, this drops to 1.68 infectious bites per person per night. With larviciding, infectious bites drop to 0.39 infectious bites per person per night (Ulrike Fillinger). During the main malaria transmission season, the incidence rate of new parasite infections was 2.9 times (95% CI: 2.0–4.3) higher in children from areas without larviciding (Ulrike Fillinger).

  - Repellents: DEET or other effect repellents need to be used to fill the gap in protection between sunset and bed time. The use of repellents has been proven effective and repellent use would fill a final gap in prevention.

- **Mandatory testing and complete treatment**: Without extensive malaria testing and treatment, there is no hope for eliminating the human pool of disease. Without testing, there can be no treatment. Thus, universal, inexpensive, and frequent testing needs to be developed and mandatorily implemented. If a person tests positive, it is critical to fully treat that individual. This should target 100% implementation at the community level and prioritize areas with the highest endemicity. In the future, development of a long acting, one dose, depot, injectable drug or drug mix would be optimal to provide ease and completeness of treatment. Mandatory testing and complete treatment is a priority in malaria eradication.
- **The Americas and Europe:** The Americas and Europe are the only realistic targets for immediate and short term malaria eradication with current technologies, the current funding of $650 million per year, and with the previously outlined priorities for a regional approach. At an approximate cost of $5 per person for the first 2-4 years (with price per person decreasing after this) and with the lower endemicity rates and population in these locations, malaria could realistically be eradicated off these three continents in the next 5-10 years. Because of the economics of the Americas and Europe, the current strategies are also more likely to be effective and sustainable. Research has proven that the recommended, integrated prevention approach will require government subsidies, infrastructure, and regulation to be effective…the same thing that would never allow this to be an effective strategy in Africa or Asia.
- **Advanced malaria vaccine development and funding:** Without philanthropic gifts from the Gates', there would only be approximately $25 million per year dedicated to vaccine research. Because it is neither cost effective, nor possible to ever eradicate malaria from Africa and Asia (1.3 billion people at risk) with the current technologies, a vaccine is the only hope. Luckily, researchers are on the verge of an effective vaccine. By only targeting the Americas and Europe with the current prevention/treatment technologies, there will be $150 million-$200 million per year to dedicate to malaria vaccine research and development. This should allow an effective vaccine to hit the market within 4-6 years. Although it seems shocking, pulling funds from Africa now, investing these funds into vaccine development, and then rolling out the vaccine with the current vaccine infrastructure in Africa and in Asia, will save more lives and allow the world to be free of malaria far sooner than if the status quo is maintained.

When tackling and addressing huge, complicated, controversial issues it is easy to let the status quo, past policies, and emotions sway ones suggestions for new policy. When developing an optimal policy suggestion it is helpful to start only with the facts, as if it was time zero and there is no current policy. When approaching the problem this way, we see we have a huge world problem; current technologies that are sufficient, but costly and not optimal; and 10% of funds required to fix the current problem with the current technologies. There is only one option if we are to ensure there is no wasted capital and that our progress is long term and sustainable. Malaria can and will be eliminated from South America, North America, and Europe within a decade. Under the suggested strategy, malaria vaccine development for the benefit of Africa, Asia, the Pacific, and the Middle East will take a priority that is ten times greater than today. With a $150 million vaccine commitment the first year and $200-$250 million commitments every year thereafter, a successful malaria vaccine could be expected within the next 4-6 years. After development, the malaria vaccine can piggyback on a 90% effective infrastructure at no cost. A zero dollars funding infrastructure, all funding will be directed towards disease treatment and prevention\. With this strategy, it would be feasible make significant strides towards malaria prevention by 2015 and eradication by 2025. With a 90% funding shortfall, the WHO will not reach their eradication goals within 50 years.

Works Cited

Brown, Hannah. "New Optimism over Malaria Vaccine Research." The Lancet (2007): 84.

Gerry F. Killeen, Thomas A.Smith. "Exploring the contributions of bed nets, cattle, insecticides and excitorepellency to malaria control: a deterministic model of mosquito host-seeking behaviour and mortality." Royal Society of Tropical Medicine and Hygiene (2007): 101, 867—880.

Hargreaves, Sally. "Malaria advances still not reaching patients, warns charity." The Lancet (2008): (8)667.

Hay, et al. "A World Malaria Map: Plasmodium falciparum Endemicity in 2007." PLoS Med (2009): 6(30).

Ian M Hastings, Eline L Korenromp, Peter B Bloland. "The anatomy of a malaria disaster: drug policy choice andmortality in African children." Lancet Infect Dis (2007): 7:739-748.

Krogstad, Donald J. "Chapter 366- MALARIA." Goldman. Goldman: Cecil Medicine, 23rd edition. Oxford: Saunders, 2007. Chapter 366.

Lancet. "The Gates' Billions: Where next for malaria?" The Lancet Infectous Diseases (2008): 269.

Marchant, et al. "Assessment of a national voucher scheme to deliver insecticide-treated mosquito nets to pregnant women." CMAJ (2010): 182(2): 152-156.

Miller, John M., et al. "Estimating the number of insecticide treated nets required by African households to reach continent-wide malaria coverage targets." JAMA (2007): 297(20):2241-2250.

Morris, Kelly. "Substantial Progress made in Malaria Reseach, say experts." The Lancet (2009): 81.

N Hill, A Lenglet, A M Arnez. "Plant based insect repellent and insecticide treated bed nets to protect against malaria in areas of early evening biting vectors: double blind randomised placebo controlled clinical trial in the Bolivian Amazon." BMJ (2007).

Nierengarten, Mary Beth. "First trial results of a blood-stage malaria vaccine promising." The Lancet (2008): (8)152.

Pawledge, Tabatha M. "Engineering a Malaria Resistent Mosquito." The Lancet (2007): 311.

"The global malaria action plan." RBM. World Health Organization. Geneva: WHO, 2008. www.rollbackmalaria.org/gmap.

Senior, Kathryn. "Funding scrutiny could help set priorities for malaria." The Lancet (2008): 8:280.

Ulrike Fillinger, Bryson Ndenga, Andrew Githeko & Steven W Lindsay. "Integrated malaria vector control with microbial larvicides and insecticide-treated nets in western Kenya: a controlled trial." Bull World Health Organ (2009): 87:655–665.

UN. World Population Prsopects: The 1998 Revision. Volume I: Comprehensive Tables. New York: United Nations, 1999.

Wakabi, Wairangala. "Big Hurdles Remain in Africa's Fight Against Malaria." The Lancet (2010): (10)10.

WHO. World Malaria Report. WHO publication. Geneva: World Health Organization, 2009.

Appendix

Chapter 2.
Policies, strategies and targets for malaria control

This chapter summarizes the policies, strategies and targets for malaria control recommended by WHO. It includes three sections: 1) diagnosis and treatment of malaria; 2) malaria prevention by mosquito control; and 3) goals, indicators and targets.

2.1 Diagnosis and treatment of malaria, including preventive treatment

The two main objectives of an antimalarial treatment policy are:

1. to reduce morbidity and mortality by *i)* ensuring rapid, complete cure of the infection and thus preventing the progression of uncomplicated malaria to severe, potentially fatal disease, *ii)* malaria-related anaemia and, during pregnancy, *iii)* the negative impact of malaria on the fetus; and
2. to curtail the transmission of malaria by reducing the parasite reservoir of infection and infectivity.

Current WHO recommendations for diagnosis and treatment are shown in **Box 2.1**. Since publication of the *World Malaria Report 2008*, WHO has made several modifications to its malaria policy recommendations *(1)*:

i) Prompt parasitological confirmation by microscopy or alternatively by rapid diagnostic tests (RDTs) is recommended for all patients with suspected malaria before treatment is started. Treatment solely on the basis of clinical suspicion should be considered only when a parasitological diagnosis is not accessible.

ii) A fifth ACT, dihydroartemisinin-piperaquine, has been added to the treatment options.

iii) A single dose of primaquine is recommended in addition to ACT as an anti-gametocyte medicine in treatment of *P. falciparum* malaria, particularly as a component of a pre-elimination or an elimination programme, provided the risks for haemolysis in glucose-6-phosphate dehydrogenase (G6PD)-deficient patients have been considered.

Furthermore, in light of evidence of resistance to artemisinins, WHO urges more strongly the continued routine monitoring of therapeutic efficacy of antimalarial medicines and halting the use all monotherapies for the treatment of uncomplicated malaria *(2)*.

BOX 2.1

WHO recommendations for diagnosis and treatment of malaria

- Prompt parasitologic confirmation by microscopy or alternatively by rapid diagnostic tests (RDTs) is recommended in all patients suspected of malaria before treatment is started. Treatment solely on the basis of clinical suspicion should only be considered when a parasitological diagnosis is not accessible.
- Uncomplicated *Plasmodium falciparum* malaria should be treated with an artemisinin-based combination therapy (ACT); vivax malaria should be treated with chloroquine where it is effective, or an appropriate ACT, in areas where *P. vivax* resistance to chorloquine has been documented. Both chloroquine and ACTs should be combined with primaquine for 14 days in the treatment of *P. vivax* malaria, for the prevention of relapses, subject to considering the risk of haemolysis in patients with G6PD-deficiency.
- Five ACTs are currently recommended for use: artemether-lumefantrine, artesunate-amodiaquine, artesunate-mefloquine, artesunate-sulfadoxine pyrimethamine, and dihydroartemisinin-piperaquine. The choice of the ACT should be based on the efficacy of the combination in the country or area of intended use.
- Artemisinin derivatives should not be used as monotherapies for the treatment of uncomplicated malaria as this will promote resistance to this critically important class of antimalarials.
- A single dose of primaquine to be added as an anti-gametocyte medicine to ACT treatment of *P. falciparum* malaria, particularly as a component of pre-elimination or elimination programme, is recommended provided the risk of haemolysis in G6PD-deficient patients is considered.
- Severe malaria should be treated with a parenteral artemisinin derivative or quinine to be followed by a complete course of an effective ACT as soon as the patient can take oral medications. When intravenous or intramuscular treatment is not feasible, e.g. in peripheral health posts, patients should receive pre-referral treatment with an artemisinin suppository and be transferred to a health facility capable of providing definitive treatment with parenteral antimalarial medicines.
- In settings with limited health facility access, diagnosis and treatment should be provided at community level through a programme of community case management (home-based management) of malaria.

2.2 Malaria prevention through mosquito control

2.2.1 Aims

Malaria vector control is intended to protect individuals against infective mosquito bites and, at the community level, to reduce the intensity of local malaria transmission. The two most powerful and most broadly applied interventions are insecticide-treated nets (ITN) and indoor residual spraying (IRS). In some specific settings and circumstances (if the breeding sites are few, fixed, and easy to identify) these core interventions may be complemented by other methods such as larval control or environmental management. WHO recommendations for vector control are the following:

1. Because high coverage rates are needed to realize the full potential of either ITNs or IRS, WHO GMP recommends "universal coverage" of all people at risk in areas targeted for malaria prevention. In the case of ITNs, this means that all people at risk in areas targeted for malaria prevention should be covered with ITNs *(3, 4)*.
2. ITNs should be either free of charge or highly subsidized. Cost should not be a barrier to making them available to all people at risk, especially young children and pregnant women *(3)*.
3. Universal coverage with long-lasting insecticidal nets (LLINs) can be achieved and maintained by combining distribution through occasional campaigns with continuous distribution to pregnant women and infants at routine antenatal and immunization contacts *(3)*.
4. Only LLINs recommended by the WHO Pesticide Evaluation Scheme (WHOPES) should be procured by national malaria programmes and partners for malaria control. These nets are designed to maintain their biological efficacy against vector mosquitoes for at least three years in the field under recommended conditions of use, obviating the need for regular insecticide treatment *(5, 6)*.
5. IRS consists of the application of insecticides to the inner surfaces of dwellings, where endophilic anopheline mosquitoes often rest after taking a blood meal *(4)*. IRS is applicable in many epidemiological settings, as long as operational and resource feasibility is considered in policy decisions. Twelve insecticides belonging to four chemical classes are currently recommended by WHO for IRS. An insecticide for IRS in a given area is selected on the basis of data on resistance, the residual efficacy of the insecticide, cost, safety and the type of surface to be sprayed. Special attention must be given to preserving susceptibility to pyrethroids, because they are the only class of insecticide currently used on ITNs.
6. Scientific evidence indicates that IRS is effective in controlling malaria transmission and thus reduces the related burden of morbidity and mortality as long as most houses and animal shelters (e.g. > 80%) in targeted communities are treated. IRS is effective only if the operation is performed correctly, which depends on the existence at national, provincial and district levels of adequate infrastructure and programme capacity for implementation, monitoring and evaluation *(4)*.
7. DDT has comparatively long residual efficacy (≥ 6 months) against malaria vectors and plays an important role in the management of vector resistance. Countries can use DDT for IRS for as long as necessary and in the quantities needed, provided that the guidelines and recommendations of WHO and the Stockholm Convention are met and until locally appropriate, cost-effective alternatives are available for a sustainable transition from DDT *(7)*.
8. Resistance to insecticides, especially pyrethroids, is an urgent and growing threat to the sustainability of current methods of vector control. Monitoring and managing resistance to the insecticides used in both ITNs and IRS are vital *(3, 4)*.
9. In most settings where IRS has been or is being deployed, ITNs or LLINs are already in use. Neither LLINs nor IRS alone will be sufficient to achieve and maintain interruption of transmission in holoendemic areas of Africa or in hyperendemic areas in other regions *(3)*. Some observational evidence indicates that the combination of IRS and LLIN is more effective than either intervention alone, especially if the combination helps to increase overall coverage with vector control *(8)*. More formal trials are being planned. In using the combination of IRS and ITNs, it is preferable to use a non-pyrethroid insecticide for IRS.

2.2.2 Resistance to antimalarial drugs

Antimalarial drug resistance is a major public health problem, which hinders the control of malaria. The rapid spread of resistance to these drugs over the past few decades has led to intensification of the monitoring of their efficacy, to ensure proper management of clinical cases and early detection of changing patterns of resistance in order to revise national malaria treatment policies. Surveillance of therapeutic efficacy over time is an essential component of malaria control. The results of tests for therapeutic efficacy (in vivo tests) provide the most important information for determining whether first- and second-line drugs are still effective and also provide evidence for ministries of health to update their national malaria treatment policies.

WHO's role in the global management of drug resistance has been twofold. Its normative and standard-setting role results in a harmonized approach to this global concern. In order to interpret and compare results within and between regions, and to follow trends over time, tests must be conducted with similar standardized procedures, and WHO has standarded the available methods. Since 1996, WHO has updated the protocol for assessing antimalarial drug efficacy on the basis of expert consensus and feedback from the field *(9)*. WHO has also prepared a field manual on *in vitro* assays for the sensitivity of malaria parasites to antimalarial drugs *(10)* and a guideline on genotyping malaria parasites to distinguish between reinfection and recrudescence during therapeutic efficacy tests. Genotyping is now becoming mandatory with the longer follow-up of patients *(11)*. Apart from its normative role, WHO GMP is also providing technical assistance to countries in both the surveillance of drug resistance and guidance on treatment policies. Routine surveillance systems put in place by countries and coordinated by WHO have shown that the failure rate of currently used ACTs is increasing on both sides of the Thai-Cambodian border, due mainly to local emergence of resistance to artemisinin derivatives. WHO is investigating this problem and implementing strategies to contain and prevent the dissemination of resistance further.

In response to the challenge posed by the emergence of resistance to antimalarial drugs, WHO has established a global database of information and the results of antimalarial drug efficacy tests at country

level. The database is used by governments to review and update their treatment policies. The continuously updated database can also be made available to other stakeholders. The data will be analysed for a report on global monitoring in 2009, focusing on the efficacy of ACTs, which will describe WHO's work in monitoring resistance to antimalarial drugs, setting up the database, standardizing therapeutic efficacy tests, promoting more rational use of the available tests for evaluating resistance and showing how the results of these tests are used for updating national malaria treatment policies.

2.3 Goals, indicators and targets

The vision of the RBM Partnership is "a world free from the burden of malaria" *(12)*. As of 2007, the United Nations (through the MDGs), the World Health Assembly and the RBM Partnership had consistent goals for intervention coverage and impact for 2010 and 2015 *(13–15)*. Coverage is meant to reach ≥ 80% by 2010 with four key interventions: ITNs for people at risk, appropriate antimalarial medicines for patients with probable or confirmed malaria, IRS for targeted households at risk and intermittent preventive treatment in pregnancy (in moderate-to-high transmission settings). The global impact targets are a reduction in the number of malaria cases and deaths per capita by 50% or more between 2000 and 2010, and by 75% or more between 2000 and 2015.

The RBM partnership added three additional targets as part of the Global Malaria Action Plan in September 2008 *(16)*. The first is to reduce the global number of malaria deaths to near-zero preventable deaths by 2015. This target is more aggressive than the previous target of a 75% reduction in the number of malaria deaths by 2015, although there is no global consensus on how to measure preventable deaths. The second is that malaria should be eliminated in 8–10 countries by 2015 and afterwards in all countries that are in the pre-elimination phase today (2008). The third goal is, "in the long term, eradicate malaria worldwide by reducing the global incidence to zero through progressive elimination in countries".

The Inter-agency and Expert Group on MDG Indicators has established specific indicators for malaria *(13)*:

6.6 Incidence and death rates associated with malaria.

6.7 Proportion of children under 5 years sleeping under insecticide-treated bed nets.

6.8 Proportion of children under 5 years with fever who are treated with appropriate antimalarial medicines.

Table 2.1 draws together the work of RBM since 1998, the Abuja Declaration in 2000 *(14)*, the resolution of the Health Assembly in 2005 *(15)*, and various subsequent revisions of the MDGs for malaria and the RBM Global Action Plan for Malaria. It shows practical indicators recommended by WHO for use by national malaria programmes to measure coverage with malaria control interventions and epidemiological impact. Core national operational logistics and reporting indicators are also listed. The only substantial change from last year's indicator list is the addition of a new IRS indicator: percentage of at-risk population targeted by IRS. This indicator has no target but is intended to monitor the contribution of IRS to overall malaria control.

The indicators in Table 2.1 apply to countries with high, moderate and low transmission that are in the control phase but not to those in the pre-elimination or elimination phases. Indicators have not yet been developed for the phases of pre-elimination, elimination and prevention of reintroduction.