A Micro-Level Approach to Recommendations for Combating a Potential Outbreak of a Chloroquine-Resistant Malaria (CRM) Strain in the Country of Haiti

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Abstract

Malaria is a worldwide public health burden that has been reported by the World Health Organization (WHO) to cause roughly 219 million cases of disease in 2010 with an estimated 660,000 deaths (2013). In the Caribbean nation of Haiti, malaria remains endemic. Confirmed malaria cases reported in Haiti increased from 10,802 in 2004 to 49,535 in 2009 (WHO, 2009a). Currently, P. falciparum is the predominant species to cause disease in Haiti, and unfortunately, the same species that is most likely to cause severe malaria; responsible for most malarial deaths globally (WHO, 2009a). Fortunately though, if treated early, a readily available drug, chloroquine phosphate, can effectively treat this strain. However, although chloroquine has proved to be an effective cure for nearly 40 years, the emergence and spread of chloroquine-resistant parasites are occurring both worldwide and in Haiti. The impact of these resistant cases on this already impoverished nation could be devastating. This document will outline three recommendations to serve as practical public health strategies on how to lower the risks associated with malaria, thus combating a potential outbreak of chloroquine-resistant malaria (CRM) in Haiti.

Introduction

Once the leading cause of death due to infectious agents, malaria is now ranked third after HIV and tuberculosis (Damodaran, 2013). Current World Health Organization estimates state that in 2010 there were roughly 219 million cases of disease with an estimated 660,000 deaths. These numbers are down from previous WHO estimates in 2008 of 243 million cases with 863,000 deaths. WHO places 3.3 billion people, i.e., 50% of the world population at risk of contracting malaria, with 2.1 billion at a low risk and 1.2 billion at a high risk (WHO, 2013b).

The goal of this document will be to provide recommendations for dealing with CRM in Haiti on the micro-level. Because dealing with the country of Haiti at this time is such a difficult and convoluted situation, the recommendations will focus on the micro-level.

Prior to the recommendations, an overview of malaria will be discussed with specific information on epidemiology, vectors, diagnosis, medicines available, and drug resistance. When reviewing malaria, a particular focus will be on the strain Plasmodium falciparum due to its drug resistance and the subsequent potential impact that this might play.

Malaria Overview

Malaria is a serious febrile illness that is caused by a protozoan parasite. This microorganism belongs to the genus Plasmodium. The Plasmodium parasite infects humans through the bites of infected mosquitoes, also known as “malaria vectors”.

According to the World Health Organization (WHO), there are four known Plasmodium species that cause infections in humans:

- Plasmodium falciparum
- Plasmodium vivax
- Plasmodium malariae
- Plasmodium ovale

P. falciparum and P. vivax are the two most common species; responsible for 95% of cases reported worldwide. P. falciparum is known to be the most deadly (2013).

Transmission of malaria is caused exclusively through the bite of the female Anopheles mosquito. The lifecycle of the Plasmodium parasite is quite complex and needs 10-18 days to infect its mosquito host in order to be transmitted to the human host. Malaria can cause an acute febrile illness. Symptoms generally begin 10 days to 4 weeks after infection and can range from absent or very mild to severe which can include death (WHO, 2013). The risk of malaria does not seem to be evenly distributed throughout the year. Most cases of malaria occur between November and January.

Malaria symptoms are categorized as uncomplicated or severe. An uncomplicated, classic attack lasts 6-10 hours and can consist of a cold stage (shivering); a hot stage (fever, headaches, vomiting); and a sweating stage (sweats,

tiredness). A classical attack repeats itself every second or third day depending on the Plasmodium species. This uncomplicated, classic attack can look very similar to influenza.

Severe malaria occurs when serious organ failure occurs or because of abnormalities in the patient's blood. Some of the problems of severe malaria include: cerebral malaria, severe anemia, hemoglobinuria, acute respiratory distress syndrome, abnormalities in blood coagulation, low blood pressure, acute kidney failure, hyperparasitemia, metabolic acidosis, or hypoglycemia (WHO, 2013).

Surveillance Methods

Surveillance is necessary in order to determine the severity of a disease and to meet elimination objectives. Regarding malaria, surveillance is performed for four major reasons:

1. The need for rapid detection of existing, new or reintroduced disease
2. The identifications of periods of low transmission when the disease could be responding to an elimination effort
3. Understanding of trends in incidence and prevalence or shifts in disease
4. The detection of resistance of disease to conventional forms of treatment.

Currently there are two surveillance tools that are used for malaria detection; microscopy and rapid diagnostic test (RDT). The long-term choice of which of these diagnostic tools to use; microscopy, RDT, or a combination of both, will depend on multiple factors. These factors include:

- Skills available of health care personnel

- Patient case-load
- Funds allocated
- Availability/use of microscopy for other diseases (Wongsrichanalai, 2007)

In the United States, both microscopy and RDTs are recommended, and at minimum, either test should be available at health-care facilities for malaria diagnosis. In Haiti, having a similar recommendation of implementing both RDTs and microscopy would be ideal, however this is not always practical or feasible. In many instances, neither test is available and presumptive diagnosis is used. A presumptive diagnosis identifies the likely condition a patient has, whereas a surveillance tool would be used to confirm the presence of the condition.

Presumptive diagnosis and treatment of uncomplicated malaria continues to be common in many developing countries, including Haiti, even despite well-known problems with this strategy. Clinical symptoms of uncomplicated malaria are nonspecific and overlap with several other diseases; as such, diagnosing malaria based on symptoms alone leads to substantial over diagnosis of malaria. Massive overtreatment with antimalarials is likely to be unsustainable in areas where drug resistance occurs.

Current World Health Organization (WHO) guidelines on malaria case management recommend parasitological confirmation before treatment with an antimalarial. The gold standard has for many years been microscopy. However, unless the laboratory technicians are well trained and the equipment well maintained, the accuracy of microscopy can be low under field conditions. Rapid diagnostic tests (RDTs) for malaria require limited training and have been found to perform well in

certain situations.

A major potential barrier to the use of surveillance tools for malaria is the cost of the tests. However, improved targeting of antimalarial treatment to parasite-positive patients has been found to result in substantial cost savings of antimalarial drugs, sometimes even enough to also cover the additional costs of the testing.

Rates of Disease

The most recent data released by the World Malaria Report 2012 summarizes data received from 104 malaria-endemic countries and territories for 2011. Ninety-nine of these countries had on-going malaria transmission. In this report, the WHO estimates in 2010 there were about 219 million cases of malaria worldwide. A total of 106 endemic areas were identified with Africa was the most affected continent. Africa has approximately 90% of all malaria deaths occurring there (2012).

Haiti has always been particularly vulnerable to malaria. However, the Haitian earthquake on January 12, 2010, which killed an estimated quarter of a million people and displaced over a tenth of the Haitian population, has turned the malaria situation from a proverbial festering sore to full-blown sepsis. Whereas in most places in the world, malaria is on the decline, confirmed malaria cases reported in Haiti increased. The most recent WHO report states that there were a total of10,802 in 2004. In 2009 though, this number ballooned up to 49,535 (2009b).

This dramatic increase is quite alarming. What is also alarming is that P. falciparum is the predominant species to cause disease in Haiti. And unfortunately, this

is the same species that is most likely to cause severe malaria and death.

Current Malaria Treatments

Malaria can be a treatable disease with the correct anti-parasitic medicine. The most readily available and least expensive of these medicines is called chloroquine. However, drug resistance can occur to chloroquine, which can pose a great challenge to the medical community. Such drug resistance, although not always a life threatening problem, can have devastating effects due to the lack of proper testing and the difficulty in receiving the correct medication in a timely manner.

As drug resistance develops to existing drugs, new ones need to be introduced. For Plasmodium falciparum use of two or more drugs with different modes of action in combination is now recommended to provide adequate cure rate and delay development of resistance (White, 2004).

Cloroquine-Resistant Malaria (CRM) in Haiti

Drug resistance has been well documented in two species of malarial parasites; Plasmodium falciparum and Plasmodium vivax. Of greatest concern are the rapid developments in the resistance of Plasmodium falciparum to the commonly used chemoprophylactic agent, chloroquine-phosphate. This species, which is capable of producing life-threatening disease, has shown various levels of resistance in different parts of the world. Despite evidence of failing chloroquine efficacy, little work has assessed the problem or explored alternative therapies.

Since no therapies either on the market or under development are totally

protective against malaria, there is the possibility of resistance developing to any given therapy that is developed. This is a serious concern, as the rate at which new drugs are produced by no means matches the rate of the development of resistance. In addition, the most newly developed therapeutics tends to be the most expensive and is required in the largest quantities by some of the poorest areas of the world (Baird,).

Chloroquine was the main malaria therapy worldwide from the 1940s until the 1990s. Following the emergence of chloroquine-resistant Plasmodium falciparum, most African countries, where CRM is widespread, have discontinued the use of chloroquine and now promote artemisinin-based combination therapy as the first-line treatment (CDC, 2011). Antimalarial drug resistance is a major obstacle to the control of malaria in endemic countries. For example, in 2012, Bangladesh reported an estimated 29,522 malaria episodes, of which 94% were reported as being caused by Plasmodium falciparum (van den Broek, 2004). This is alarming due to the many published studies that indicate that P. falciparum shows varying levels of resistance to chloroquine, mefloquine and sulfadoxine-pyrimethamine.

Haiti has been historically considered the outlier with no major reported outbreaks of CRM and has not needed to move to the artemisinin-based combination therapy. This is in sharp contrast to places where the P. falciparum strain has been known to reside (CDC, 2010a). However, a recent study that was performed that did show reported cases of CRM in Haiti (Londono, 2009). In 2009, Berlin L. Londono et al was able to identify CRM cases in the low-lying Artibonite Valley area of Haiti. Through passive and active surveillance, Londono was able to identify 79 P. falciparum infections out of 821 persons by using PCR for the P. falciparum gene. Of these 79

cases, 4 were identified as being CRM for a percentage of 6%. This was alarming to the medical community as it is the first cases of reported CRM in Haiti (2009).

In 2012, Ami Neuberger et al performed a follow-up study to Londono's work to look for CRM in Haiti (2012). This study looked at 49 patients with falciparum malaria in order to detect CRM. The results of this study did not detect CRM. However, this study had many flaws. First, the study was performed in Leogane, a town of 200,000 residents, located 30km west of Port-au-Prince. The Londono study was performed in Artibonite Valley which 100km north of Port-au-Prince. This change in location could show that there is a varying of disease by geographical region and not a true lack of disease. Also, the small sample size of only 49 patients could have led to a missing of disease. Finally, the way the disease was detected was through follow-up of patients after the falciparum malaria after treatment with chloroquine for 1 month. This short follow-up or incomplete follow-up time may not have been adequate to detect true CRM (2012). Based on these two studies, continued surveillance is needed in Haiti to rule out and prepare for the emergence of CRM.

Factors Effecting Malaria Control

Many factors combine together to affect the health of individuals and communities. These factors, known as determinants of health, play a major role in determining whether a person is healthy or not. According to the World Health Organization, there are seven determinants of health. These determinants are:

1. Income and social status/poverty
2. Education
3. Physical environment

4. Social support
5. Genetics
6. Health services
7. Gender (WHO, 2013a)

While all these seven play a major role in the health of the Haitian people, two of these determinants seem to play the largest and most major roles in the current malaria problem; income and social status/poverty and health services. Ultimately these determinants will determine the recommendations for malarial control.

Income and Social Status/Poverty

Haiti has occupied the unenviable position of being the poorest nation in the Western Hemisphere for decades. Income per capita ranges from US $400 to US $560 with 54% of Haitians living on less than US $1 a day and 78% living on less than US $2 a day. Rural Haitians income per capita is even less; coming in at US $100 (UNICEF, 2013). The effect of living in poverty ultimately has a dramatic impact on health, putting developing communities at risk through the increased sharing of limited space, lack of education on health issues, lack of healthcare, lack of housing, inadequate food and clean water, and exposure to vectors that can spread disease.

Health Services

In terms of health care spending, Haiti ranks last in the western hemisphere (Alfred, 2012). Economic instability has limited any growth in this area. Per capita, Haiti spends about US$83 annually on health care. Most rural areas have no access to health care, making residents susceptible to otherwise treatable diseases. Only one-

fourth of births are attended by a skilled health professional (US Library of Congress, 2006).

Obtaining accurate numbers of currently open and functioning Haitian hospitals is extremely difficult. However, current estimates show that there are between 30-40 hospitals currently open nationwide to take care of the needs of 10.17 million people. The average rate of physicians per 100,000 population is also difficult to determine. However, the United Nations reports this number as 25 physicians per 100,000 population (Henry J Kaiser Foundation, 2013) (United Nations, 2008). While this is not the lowest in the world, it is considerably low.

Furthermore, of the few hospitals that do exist, these hospitals are unfortunately inadequate in order to take care of the needs of the Haitian people due to the sheer volume of patients. The Haitian hospitals lack the sufficient medical staff, support staff, training, equipment and treatment. The largest public hospital, Haiti's University and Educational Hospital (HUEH), was partially damaged in the earthquake with 150 nursing students killed and two-thirds of the buildings destroyed (Partners in Health, 2010).

Recommendations

Diverse opinions have emerged about the best way to scale up malaria interventions. Three controversies/questions seem most important and were used when considering the following proposed recommendations. These controversies/questions are:

(1) Should the recommendation focus on a broader target of febrile illness, or be specific to malaria only?

(2) Should the recommendation feature a single intervention or be targeted at a much broader situation or an entire determinant of health?

(3) Should the recommendation have a preference for a single delivery method or focus on multiple methods? (Gaumer, 2013)

1. Creating sustainable health care opportunities on the local level

Provisions essential to the control of malaria include the delivery of fast primary care where health care staff is well trained and supported with the necessary supplies for efficient treatment. However, in Haiti, this is a major issue due to the lack of medical staff. Due to this, providing adequate health care job opportunities and career development to the long-term success of revamping the local Haitian health care system is difficult. Currently, there is insufficient health care staff in Haiti to help provide medical care at the local level. Reasons for this include: lack of job opportunities (hospitals), need to gain advanced training outside of Haiti, and poor wages in the health care industry (Haar, 2012). These are the same reasons why local health care professionals choose to migrate outside of Haiti. Health professionals who leave for training but return may have the needed skills to help, but do not have the needed infrastructure and support to practice their trade. Therefore, those that do receive training tend to leave for other opportunities in other locations rather than staying to help their local neighbors.

There is also the problem of physicians/health care workers from high-income countries coming to Haiti. Although these physicians/health care workers try to help make a difference, long-term damage can occur to what little health care infrastructure does exist in Haiti.

When high-income physicians come to Haiti to help see patients, the Haitians lose respect for the local Haitian trained health care staff, looking down on them as inferior. As this begins to happen, no matter how well meaning or energetic, the brief tenure of the high-income country doctors do not create a system that helps from within.

Acknowledging this issue is therefore an actual part to the solution. Although high-income physicians feel the need to travel to Haiti to provide medical care, a strong recommendation should be that these physicians focus their resources on teaching and training the local Haitian health care providers rather than treating and healing Haitian patients. This will require cooperation and coordination with the existing infrastructure.

Because local Haitian providers are the backbone of the health-care sector, it is vital for all actors to create an active dialogue on this issue. There will certainly be difficulty in accessing and motivating private providers to tackle the management of impoverished communities that may not be able to pay sufficiently, but creative solutions such as subsidizing care for poor people within the private system have been utilized in some situations and may prove useful in Haiti. As Haiti rebuilds over the next several years, local, governmental and international organizations must leverage the enormous potential of the providers already present to more equitably distribute work and create a more effective health-care infrastructure.

2. **Early recognition of malaria utilizing malaria RDTs to minimize CRM impact**

A more practical approach to helping control and eliminate CRM is through providing and utilizing malaria RDTs. For many years the only malarial test approved in

the Haitian national policy for the diagnosis and management of malaria was microscopy. However, the use of microscopy often was limited by lack of equipment or trained personnel. In contrast, malaria RDTs require less equipment or training to use. RDTs were not incorporated into the MSPP malaria control strategy because of concerns that these newer tools, when compared with microscopy, would not be sufficiently sensitive and would be difficult to sustain in some settings in Haiti. However, after the earthquake, the acute need for clinical services and malaria diagnostics, and the presence of international nongovernmental organizations assisting with the response, MSPP allowed the temporary use of RDTs.

Following the temporary usage of RDT's, the MSPP and CDC compared the performance of expert microscopy with the performance of two brands of RDTs introduced temporarily in Haiti for malaria diagnosis. Four health facilities were included in the assessment.

Based on these findings the MSPP adopted the use of RDTs as part of the national strategy at the following health facilities:

- Health centers and clinics without microscopy capacity; and
- Departmental hospitals, community referral hospitals, and specialty hospitals during laboratory off-hours or if microscopy is not available (CDC, 2010b).

RDTs can increase the early recognition of malaria when the availability of laboratory-based diagnosis is not available. This therefore will help to improve the overall management of febrile patients in malaria endemic areas.

This application has been studied and used throughout the world in situations similar to Haiti. For example, in preparation to scale-up the usage of RDTs in health facilities in Malawi, an evaluation of four RDTs was conducted to help guide national-level decision-making was conducted. Combined with other published data and global recommendations, the results of this evaluation have subsequently been used to increase national uptake. Effectiveness was measured as the number and proportion of patients correctly diagnosed and treated. Incremental Cost-Effectiveness Ratios (ICERs) were estimated from the societal perspective. In this particular study, RDT usage was most cost-effective with lowest ICER US$5.0 compared to microscopy US$9.61 per case correctly diagnosed and treated. In the high transmission setting, ICER was US$4.38 for RDT and US$12.98 for microscopy. The corresponding ICERs in the low transmission setting were US$5.85 and US$7.63 respectively (Lauer, 2010).

3. **Utilize public sources to distribute malarial medicines when external sources are inadequate**

Ensuring that the poor and vulnerable populations benefit from malaria control interventions remains a challenge for all malaria endemic countries. Providing long term, sustainable health care programs that seek ethical partnerships with community leaders, while introducing a consensus community engagement can build relationships that will help to prioritize the health needs in local cities/villages. This community engagement model can be used to educate villages on the importance to recognize malaria as it occurs. Creating strategies for preventing infections have shown to have substantial effect on the potential rate of development of resistance.

Until recently, ownership and use of insecticides treated nets (ITNs) in most countries was low and inequitable. However, coverage has increased in countries where free ITN distribution is integrated into mass vaccination campaigns. In Kenya, free ITNs were distributed to children aged below five years in 2006 through two mass campaigns. High and equitable coverage were reported after the campaigns in some districts, although national level coverage remained low, suggesting that understanding barriers to access remains important (Chuma, 2010).

Although there may not be an ideal situation to bring in outside public sources, an approach, such as the one seen in Kenya, can serve as a potential recommendation for Haiti. Further, this type of approach seems to make the most sense in situations where dire needs are not being met, as is currently seen in Haiti. It is because of this reason that there should be a recommendation for using various public methods of obtaining outside resources.

Another more widely used method, which has been recently seen in Haiti, has been with the use of public, Non-Governmental Organizations (NGOs). One medical benefit that NGOs have provided regarding malaria has been through their ability to purchase malarial drugs through the open market from sources not officially related to the Haitian health care industry.

This such public method has been utilized in other parts of the world and in Haiti, since the earthquake. Although the evidence shows that there is no short cut to investing in training and supervision of providers, or in treating malaria through Haitian health care workers, there have been recent publications that have shown that the

public sector has made progress in prevention and treatment in many countries (Kamal-Yanni, 2012). These studies have highlighted that the public NGO outlets face challenges in delivering their services, however, their role should be recognized and expanded in a limited role.

Conclusion

As discussed, malaria is a major public health problem and therefore it needs the adequate focus of both public health officials and health care providers in order to reduce its impact. In order to do this, recommendations must be formed and steps must be taken. If these actions are not taken, then the very real possibility of a CRM outbreak can occur with the potential to have devastating effects.

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