Malaria
The Global Health Challenge

Ashley Kamiura & D. Scott Smith, M.D.
Stanford University
March 2013

Prepared as part of an education project of the Global Health Education Consortium and collaborating partners
Learning Overview

• What Is Malaria?
• History
• Global Epidemiology: Key Facts
• Vector Biology: Anopheles
• Parasite Biology: Plasmodium
• Transmission & The Life Cycle of Plasmodium
• Prevention
• Millennium Development Goals
• The Global Fight Against Malaria: Major Players
• Where Are We Right Now?
• Quiz
• Summary
What is Malaria?
What Is Malaria?

- Malaria is a disease caused by the protozoan parasite *Plasmodium*. There are 4 species of *Plasmodium* that infect humans: *P. falciparum*, *P. ovale*, *P. malariae*, and *P. vivax*.
- The parasite is transmitted to humans via infected female *Anopheles* mosquitoes.
- Symptoms include fever, chills, and flu-like illness. If left untreated, malaria can quickly become life-threatening by disrupting the blood supply to vital organs.
- Malaria is preventable and curable.
History
History

- **2700 BC**: symptoms first described in ancient Chinese medical writings.
- **340 CE**: artemisinin drug discovered in Qinghao plant in ancient China.
- In the New World, the Spanish learned of a medicinal bark used to treat fevers. That medicine is now known as the anti-malarial quinine.
- **1874**: A German chemistry student synthesized DDT (though its insecticidal properties were not discovered until later).
- **1880**: Charles Laveran, a French army surgeon, discovered parasites in the blood of a sick soldier. Awarded Nobel Prize in 1907 for this discovery.

Source: http://www.cdc.gov/malaria/history/index.htm
Photo: Claire Parfrey
History (cont)

- **1897**: Ronald Ross, a British officer in the Indian Medical Service, demonstrated that malaria parasites could be transmitted from infected patients to mosquitoes. He also showed that mosquitoes could transmit the parasites from bird to bird, demonstrating the existence of a sporogonic cycle (development within the mosquito). For his discovery, Ross was awarded the Nobel Prize in 1902.

- **1899**: Italian investigators demonstrated human transmission by feeding mosquitoes on an infected patient, then feeding them on two uninfected volunteers, both of whom developed malaria.
1906: Camillo Golgi, an Italian physician, established the existence of multiple forms of malaria based on fever periodicity and cause of fevers. He was awarded the Nobel Prize in 1906 for this discovery.

1934: Chloroquine was discovered in Germany, though it wasn’t recognized as an effective anti-malarial until 1946.

1939: The insecticidal properties of DDT were discovered and used for malaria control at the end of WWII. Its introduction caused a huge decline in malaria (outside of Africa) in the 1940s, but the development of DDT resistance and its banishment caused a resurgence in the 1970s.
History (cont)

• **1951**: Malaria was considered eliminated in the U.S.

• **1955**: The World Health Organization submitted a proposal for the eradication of malaria worldwide. Though some progress has been made, barriers to success caused the focus of the campaign to shift from eradication to control. That effort continues today.

Source: Centers For Disease Control And Prevention
Global Epidemiology: Key Facts
In 2010, malaria was endemic in 106 countries around the world:
In 2010, there were 24 million confirmed cases of malaria and 325,000 deaths reported.

However, because not all new cases nor deaths are reported, it is estimated that 216 million people became infected with malaria, while 655,000 people died from the disease. 174 million and 596,000, respectively, were in Africa alone.

More than 40% of 2010 malaria deaths occurred in the Democratic Republic of Congo and Nigeria. The countries with the next highest mortality rates are Burkina Faso, Mozambique, Cote d’Ivoire, and Mali.

86% of all malaria deaths in 2010 were in children under 5 years of age.
Global Epidemiology: Key Facts (cont)

- Climate is the main determinant of malaria distribution.
- It is concentrated in tropical and subtropical areas due to temperature, humidity, and rainfall patterns in these regions.
- Malaria distribution is a function of *Anopheles*’ survival. *Anopheles*’ eggs are deposited in pools of standing water, where they develop into adulthood in 9-12 days.
- Temperature is also especially critical. *P. falciparum* cannot complete its growth cycle within the mosquito at temperatures below 20°C (68°F).
- Generally, in warmer regions near the equator, transmission is more intense and occurs year-round.
- Global warming is expected to widen worldwide malaria distribution.

Source: Centers For Disease Control And Prevention
Vector Biology: *Anopheles*
Vector Biology

- *Anopheles* is the only species of mosquito that transmits malaria. There are 90 different *Anopheles* species. Most are carriers but not all.
- Only female *Anopheles* transmit malaria.
- *Anopheles* prefer to feed at night, typically between dusk and dawn.
- Varied competence: some species carry few parasites, others carry large numbers.

A female *Anopheles albimanus* mosquito engorged with blood while feeding on a human host. Like other *Anopheles* species, *A. albimanus* holds the major axis of the body perpendicular to the surface of the skin when blood feeding. This species is a common vector in Central America.

Photo: James Gathany, Centers For Disease Control And Prevention, 2005
Vector Biology

- Global distribution of Anopheles species that act as a vector of malaria:
Some species of *Anopheles* prefer to remain inside dwellings after feeding (*endophilic*), while others prefer to rest outdoors (*exophilic*).

Some species prefer feeding indoors (*endophagic*) while others prefer feeding outdoors (*exophagic*).

Some species prefer feeding on humans (*anthropophilic*) while others prefer feeding on animals (*zoophilic*).

Generally, *anthrophilic, endophagic* mosquitoes come into contact with humans more frequently and are therefore more effective vectors.
Parasite Biology: *Plasmodium*
There are 5 different species of the malaria parasite: *Plasmodium vivax*, *P. falciparum*, *P. ovale*, *P. malariae*, and *P. knowlesi*.

- The life cycles of *P. vivax* and *P. ovale* include a dormant liver stage.
- *P. vivax* predominates in most parts of the world.
- Infection with *P. falciparum* is the most serious.

Transmission & The Life Cycle of *Plasmodium*
Transmission & The Life Cycle of *Plasmodium*

- Transmission of the parasite occurs when an infected female mosquito feeds on a human.
- The life cycle of *Plasmodium* (see Supplementary Note on next page) is as follows:

![Diagram of Plasmodium life cycle](www.biology-forums.com)
Supplementary Note: The Life Cycle of Plasmodium

Malaria parasites are spread by infecting two hosts: humans and female Anopheles mosquitoes.

If an uninfected mosquito feeds on an infected human, she will take in blood containing male and female gametocytes. The gametocytes will then mature inside the mosquito and undergo sexual reproduction to form a zygote, which after passing through several developmental stages, eventually results in the production of a large number of sporozoites (“sporogony”). The sporozoites wander throughout the body of the mosquito, including the salivary glands, where they will be inoculated into the next person on which she feeds.

In humans, the parasites leave the blood vascular system and invade the parenchymal cells of the liver, where they undergo asexual multiplication (“shizogony”). Rupture of the hepatic cells releases merozoites into the circulation, where they can then invade red blood cells (RBCs). In RBCs, the parasites continue to divide and cause the cells to burst, releasing merozoites that continue the cycle and invade other RBCs. This stage of the life cycle causes symptoms of chills and fever in the infected individual. Merozoites develop into gametocytes within RBCs, where they can be ingested by a feeding mosquito.
Prevention
Prevention

- Key interventions to control malaria include bed nets, insecticides, and drugs.
- **Long lasting insecticide treated bed nets (LLINs)**
  - Provide a physical barrier between humans and mosquitoes during the time of day mosquitoes are most likely to transmit malaria – at night.
  - Cost per person for one year of protection by an LLIN: **$1.39 USD**.
  - Spraying this imperfect barrier with insecticide will kill a mosquito before it can find a way past the net.
  - For maximum effectiveness, regular bed nets must be re-treated with insecticide every 6 months. Due to the logistical infeasibility of this requirement in rural areas, LLINs were developed and can provide protection for up to 5 years.

Source: Roll Back Malaria Campaign
Photo: Antonio Matimbe/World Vision

Children sit under an LLIN in Ghana.
Prevention

- **Artemesinin-Based Combination Therapy (ACT)**
  - The current course of treatment for malaria-infected individuals.
  - Cost of single *adult* course of ACT treatment: **$0.90 - $1.40 USD**.
  - Cost of single *child* course of ACT treatment: **$0.30 - $0.40 USD**.
  - Resistance has been detected in 4 countries in Southeast Asia.
  - Effective and well-tolerated by patients, but due to high cost, patients often purchase cheaper, less effective, poor quality, or counterfeit drugs, leading to ACT-resistant strains of *Plasmodium*.

- **Indoor Residual Spraying (IRS)**
  - The spraying of insecticides on the interior walls of dwellings.
  - WHO currently advises the use of 12 different insecticides, including DDT, permethrin, and deltamethrin.
  - Mosquito resistance to insecticides has been detected in 64 countries.

Source: Roll Back Malaria Campaign; World Malaria Report 2012
Photo: Agfax

Indoor residual spraying in Ethiopia.
Prevention

- **Rapid Malaria Diagnostic Tests (RDTs)**
  - A.K.A. “Dipsticks,” assist in the diagnosis of malaria by providing evidence of the presence of the parasite in the blood obtained from a finger prick.
  - Cost for a single RDT: $0.50 USD.
  - Work by detecting specific antigens produced by the parasite.
  - A reliable alternative to diagnosis by microscopy when microscopy not readily available.

- **Malaria Vaccine**
  - Currently, there is no vaccine to prevent malaria, but this is an active field of research.
  - In recent Phase III clinical trials, the RTS,S vaccine had lower-than-desired efficacy, but the trials did prove it is possible to vaccinate against a parasite.
  - Current vaccine candidates target specific groups. Ultimately, more efficacious second-generation vaccines that can protect entire populations will be required.

Sources: Roll Back Malaria Campaign; The Bill & Melinda Gates Foundation
Millennium Development Goals
Millennium Development Goals

• In September 2000, all 191 member countries of the United Nations signed the Millennium Declaration, which contained eight goals surrounding poverty, hunger, disease, illiteracy, environmental degradation, and discrimination against women. The target date for achieving these Millennium Development Goals is 2015.

• Millennium Development Goal 6C is “to have halted by 2015 and begun to reverse incidence of malaria and other major diseases.”

• In a 2007 resolution, the World Health Assembly defined this reversal of malaria incidence as a 75% reduction of the global malaria burden.

• Who is working to achieve this goal?

Source: World Health Organization
The Global Fight Against Malaria: Major Players
The Global Fight Against Malaria – Major Players

The Bill & Melinda Gates Foundation (B&MGF)

- Long term goal is to eradicate the disease
- Approach includes:
  - Developing a preventive malaria vaccine by 2025 that will be safe for children and pregnant mothers
  - Developing more effective drugs and diagnostics that are cheaper for people of poor countries
  - Developing new tools to control mosquitoes, including looking into new active ingredients and products that combat insecticide resistance
  - Research the effectiveness of malaria interventions, including delivery methods
- In 2011 alone, awarded $200M in grants supporting malaria eradication efforts

Source: The Bill & Melinda Gates Foundation
Photo: Larry Hollon

Bill and Melinda Gates being interviewed at the 2011 Malaria Forum.
The Global Fight Against Malaria – Major Players (cont)

**The Bill & Melinda Gates Foundation (B&MGF)**

- Among numerous other grants, in 2012 the B&MGF awarded:
  
  - **$1.5M** to the Malaria Consortium to develop a sustainable community delivery model of Seasonal Malaria Chemoprevention.
  
  - **$3M** to WHO to establish a “situation room” to assist the 10 sub-Saharan Africa countries with the highest number of malaria cases and deaths. The situation room will work to resolve bottlenecks in financing, supply, scale up of interventions, and public health impacts.
  
  - **$7.7M** to the Harvard School of Public Health to develop diagnostic tools using genotyping and sequencing technologies, based on the population genetics of malaria parasites.
  
  - **$5M** to the Menzies School of Health Research for research on the safe, global deployment of the drug primaquine and the radical cure of *P. vivax*.
  
  - **$750M** to the Global Fund to Fight AIDS, Tuberculosis, and Malaria.

Source: The Bill & Melinda Gates Foundation
Photo: Forbes
The Global Fight Against Malaria – Major Players (cont)

**The Global Fund to Fight AIDS, Tuberculosis, and Malaria (GF)**

- An international financing institution dedicated to attracting and disbursing resources to preventing and treating the world’s three most deadliest diseases.
- Holds grant recipients accountable to strict standards that require specific targets to be reached throughout the life of the grant.
- Channels 50% of the global funding for malaria.
- Since its inception in 2002, the GF has provided 310 million bed nets, provided IRS in 44 million dwellings, and has financed ACT treatment for 260 million cases.

Source: The Global Fund
The Global Fight Against Malaria – Major Players (cont)

*World Health Organization (WHO)*

- Administers the Global Malaria Programme (GMP), which convenes experts to review evidence and set global policies, providing the benchmark for international malaria programs and multilateral funding agencies.

**WHO Global Malaria Programme: four key roles**

1. Set, communicate and promote the adoption of evidence-based norms, standards, policies, and guidelines
2. Keep independent score of global progress
3. Chart the course for malaria control & elimination
4. Develop approaches for capacity-building, systems strengthening, and surveillance
5. Identify threats to malaria control and elimination as well as new opportunities for action

Source: World Health Organization
The Global Fight Against Malaria – Major Players (cont)

Roll Back Malaria (RBM)

- The RBM partnership was launched in 1998 by WHO, UNICEF, UNDP, and the World Bank in an effort to provide a coordinated global response to the disease.
- RBM’s vision is a world free from the burden of malaria.
- At the MDG Malaria Summit in September 2008, world leaders and the global malaria community gathered in New York to endorse the Global Malaria Action Plan (GMAP), which provides a global framework for action around which partners can coordinate their efforts in meeting the 2015 MDGs.

“I believe that if you show people a problem, and then you show them the solution, they will be moved to act. The Global Malaria Action Plan lays out an achievable blueprint for fighting malaria – now it’s time for the world to take action.”

– Bill Gates, Co-Chair, Bill & Melinda Gates Foundation

Source: Roll Back Malaria Campaign
Where Are We Right Now?
Where Are We Right Now?

• The past 5 years have seen an impressive increase in international funding for malaria control efforts.

• Over the past decade, an estimated 1.1M malaria deaths were averted as a result.

• 50 countries are currently on track to reduce their malaria incidence rates by 75%, in line with the Roll Back Malaria Campaign’s targets for 2015.

• However, these 50 countries account for only 3% of the total estimated malaria cases worldwide.

Source: World Malaria Report 2012
Photo: www.futurity.org
Where Are We Right Now?

• International targets will not be met unless considerable progress is made in the 14 countries with the highest malaria burden, which account for an estimated 80% of malaria deaths.

• Unfortunately, current funding falls short of what is needed to reach the Millennium Development Goals by 2015. An estimated $5.1B USD is required *each year* between 2011 and 2020 to achieve universal access to malaria interventions.

• Presently, only $2.3B USD is available.

• We have come a long way in the fight against malaria since 1955, but to reach the Millennium Development Goals new funding sources must be identified to further scale up and sustain current efforts.

“...The daily work of rolling out malaria control programmes is invisible; it’s not front page news. Success in malaria control between now and 2015 will hinge on the hard work by unsung heroes in endemic countries — especially in district health facilities and at the community level. That’s where the battle will be won or lost, and WHO’s role is to support that work.”

Robert D. Newman, Director of GMP

Source: World Malaria Report 2012
Quiz

See if you can answer the following 8 questions. Each question is followed by the correct answer, shown in green.
What are some challenges faced by malaria vaccine developers?

a) Antigens produced by the parasite differ depending on the life cycle stage it is currently in
b) Attenuated parasites sometimes exhibit abnormal behavior, such as an inability to enter hepatocytes
c) Evidence of resistance to artemesinin
d) Logistical obstacles to administering a vaccine to the general public
e) All of the above
What are some challenges faced by malaria vaccine developers?

a) Antigens produced by the parasite differ depending on the life cycle stage it is currently in
b) Attenuated parasites sometimes exhibit abnormal behavior, such as an inability to enter hepatocytes
c) Evidence of resistance to artemesinin
d) Logistical obstacles to administering a vaccine to the general public
e) All of the above
In which region of the world do the most deaths from malaria occur each year?

a) China and India, the two most populous countries
b) Southeast Asia, where resistance to anti-malarial drugs most commonly occurs
c) Sub-Saharan Africa
d) South America, which contains the Amazon and abundant standing pools of water
e) The US and Europe, where the most cases are positively diagnosed
In which region of the world do the most deaths from malaria occur each year?

a) China and India, the two most populous countries
b) Southeast Asia, where resistance to anti-malarial drugs most commonly occurs
c) Sub-Saharan Africa
d) South America, which contains the Amazon and abundant standing pools of water
e) The US and Europe, where the most cases are positively diagnosed
The malaria parasite is transmitted by which vector?

a) Reduvid bugs
b) Aedes mosquitos
c) Culex mosquitos
d) Any blood sucking insect
e) Anopheles mosquitos
The malaria parasite is transmitted by which vector?

a) Reduvid bugs  
b) Aedes mosquitos  
c) Culex mosquitos  
d) Any blood sucking insect  
e) Anopheles mosquitos
A mosquito that bites a human indoors then rests outdoors is:

a) Zoophilic, endophagic, endophilic
b) Zoophilic, endophagic, exophilic
c) Anthrophilic, endophagic, endophilic
d) Anthrophilic, endophagic, exophilic
e) Anthrophilic, exophagic, endophilic
A mosquito that bites a human indoors then rests outdoors is:

a) Zoophilic, endophagic, endophilic
b) Zoophilic, endophagic, exophilic
c) Anthrophilic, endophagic, endophilic
d) Anthrophilic, endophagic, exophilic
e) Anthrophilic, exophagic, endophilic
What is an environmental condition that may prevent the transmission of malaria?

a) High altitude  
b) Heat  
c) Desert oases containing water  
d) Availability of animal reservoirs  
e) Global warming
What is an environmental condition that may prevent the transmission of malaria?

a) High altitudes  
b) Heat  
c) Desert oases containing water  
d) Availability of animal reservoirs  
e) Global warming
Public health strategies proven to effectively control malaria include all of the following *except*:  

a) Spraying the interior walls of dwellings with insecticides  
b) Distributing mesh nets treated with insecticides meant for sleeping under  
c) Releasing genetically incompetent vectors in areas of high transmission rates  
d) Surveillance and treatment with anti-malarial drugs  
e) Targeting mosquito larva for control
Public health strategies proven to effectively control malaria include all of the following except:

a) Spraying the interior walls of dwellings with insecticides
b) Distributing mesh nets treated with insecticides meant for sleeping under
c) Releasing genetically incompetent vectors in areas of high transmission rates
d) Surveillance and treatment with anti-malarial drugs
e) Targeting mosquito larva for control
Since 2008, funding for malaria control efforts has steadily increased.

a) True
b) False
Since 2008, funding for malaria control efforts has steadily increased.

a) True
b) False
The following terms are applicable to categorizing malaria control efforts except:

a) Control
b) Pre-elimination
c) Eradication
d) Elimination
e) Prevention of re-introduction
The following terms are applicable to categorizing malaria control efforts except:

a) Control
b) Pre-elimination
c) Eradication
d) Elimination
e) Prevention of re-introduction
Malaria is a parasite that is transmitted to humans via infected mosquitoes. Malaria is preventable and curable. However, if left untreated, malaria can cause death by disrupting the blood supply to organs. It was first described in Chinese antiquity but has more recently been understood biologically using microscopes. The world’s heaviest malaria burden is in Africa. 40% of all malaria deaths in 2010 were in four African countries alone. Children under the age of 5 are the demographic most affected by malaria. In 2010, 86% of all malaria deaths occurred in children under 5 years of age.
The world’s heaviest malaria burden is in Africa. 40% of all malaria deaths in 2010 were in four African countries alone.

The distribution of malaria is a function of *Anopheles* survival, which is in turn a function of climate. *Anopheles* requires warm climates to survive. It follows, then, that malaria prevalence is highest in warmer areas near the equator, though global warming is expected to increase the lateral ranges of global malaria distribution.

Only female *Anopheles* mosquitoes transmit malaria.

There are five different species of the malaria parasite. *Plasmodium falciparum* is the most serious.
Summary (cont)

- Key interventions to malaria transmission include bed nets, insecticides, and drugs.
- Currently, no vaccine against malaria exists, though this is an active area of research.
- The Millennium Development Goals call for a reversal of the global malaria burden by 75% by 2015.
Since 2008, there has been an impressive increase in funding for malaria control efforts, and 1.1M malaria deaths were averted as a result. 50 countries are currently on track to meet the Millennium Development Goals.

However, additional funding is required in order to meet these internationally agreed upon targets. Specifically, $5.1B per year is required between 2011 and 2020, but only $2.3B is currently available.
References

**Papers**


**Books**

References (cont)

Websites

• Bill & Melinda Gates Foundation: [http://www.gatesfoundation.org/What-We-Do/Global-Health/Malaria](http://www.gatesfoundation.org/What-We-Do/Global-Health/Malaria)
• Centers For Disease Control and Prevention: [http://www.cdc.gov/MALARIA/](http://www.cdc.gov/MALARIA/)
• Roll Back Malaria: [http://www.rbm.who.int/](http://www.rbm.who.int/)
Credits

- Ashley Kamiura, BA, Stanford University
  - akamiura@stanfordalumni.org

- D. Scott Smith, MD, MSc, DTM&H
  - Chief of Infectious Disease & Geographic Medicine, Kaiser Permanente, Redwood City, California
  - Adjunct Assistant Clinical Professor Depts. of Human Biology and Medical Microbiology & Immunology, Stanford University School of Medicine
  - ssmith@stanford.edu
The Global Health Education Consortium and the Consortium of Universities for Global Health gratefully acknowledge the support provided for developing teaching modules from the:

Margaret Kendrick Blodgett Foundation
The Josiah Macy, Jr. Foundation
Arnold P. Gold Foundation

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 3.0 United States License.