Malaria

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Disclosures

• **Conflict of interest:**
  - I have no patents or financial interest in the antigens and vaccines discussed today

• **Pre-clinical:**
  - All pre-clinical work was conducted under IACUC approved protocols in AAALAC-accredited facilities

• **Clinical & Field Trials:**
  - Informed consent was obtained prior to screening and enrolment
  - Trials were conducted according to ICH and FDA guidelines

• **Non-official:**
  - All opinions expressed are personal and are not official
Overview

- Malaria is a large global problem
- Current strategies are inadequate
- DoD is making progress towards malaria solutions
- Multi-pronged efforts are ongoing
What is Malaria?

- Potentially lethal parasitic disease (*Plasmodium* species)
- Transmitted between humans (reservoir) by mosquitoes (the vector)

- **Initial malaria**: fever, chills, muscle aches, headaches, fatigue, rigors
  - ACUTE ILLNESS

- **Untreated**: severe anemia, kidney failure, coma, convulsions
  - DEATH

- **Survivors**: Often become chronic carriers
  - ILL HEALTH, LEARNING DISABLED

- RESERVOIRS OF INFECTION
History

- Chinese writings (2700 BC)
- The Eber’s papyrus (1550 BC)
- Hippocrates (described malaria fevers)
- Greek civilizations affected by “bad air”, the rich summered in the highlands
- Malaria in the United States???
  - First military expenditure in 1775 ($300) for quinine to protect G. Washington’s troops
  - In Civil War (1861-65) 50% white and 80% of black troops w/ malaria annually
The Situation is Dire

• Malaria is a personal tragedy
  – Death in infants and in 1st pregnancies
  – Sickness, long term disability, chronic illness in survivors

• Malaria is a global health tragedy
  – Malaria kills 3,000 children a day
  – Malaria hastens spread of HIV infection**

• Malaria is an economic-political tragedy
  – Major cause of disability adjusted life years (DALYS)
  – Prevents development, especially in Africa
  – A cause and a consequence of poverty

**Abu-Raddad LJ et al. Links Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa. Science 2006;314:1603-6
The Global Malaria Problem

• #1 cause of death of young African children

• Malaria is resurgent:
  – More cases now than ever in history

• Inadequate prevention:
  – Bed nets save lives - but not widely used
  – DDT/insecticides save lives – but not adequately used

• Inadequate treatment
  – Poor diagnosis -
  – Drug resistance:
    • affordable drugs not effective
    • effective drugs not affordable

• No malaria vaccine yet licensed

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ITNs – Insecticide Treated Nets

• ITNs versus no nets // protective effect
  – 50% reduction in malaria attacks
  – 45% reduction in severe malaria attack
  – 17% reduction in death

• Additional benefits
  – Improved maternal health & hematocrits
  – Improved infant health & birth weights

• Cost: about $6

• Cost effective: Yes

• Usage: Less than 10% of children at risk

• Issues:
  – Too expensive for poor users to purchase
  – Requires retreatment with insecticide
  – Requires repair
  – Requires education to promote use

Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database Syst Rev. 2004;(2):CD000363.
Indoor Residual Spraying (IRS)
DDT Use and Cumulative Malaria Cases in South America

House Spray Rates, 1965-92, and Cumulative Malaria Cases, pre- vs. post-1979
(Brazil, Colombia, Ecuador, Peru, Venezuela)

Decreasing DDT use
Increasing malaria cases

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Distribution of Malaria & Abnormal Hemoglobin Genes in Africa

- Haldane’s hypothesis explains human abnormal red cell enzymes (G6PD), hemoglobins (Hb C, Hb E, Hb S) and red cell surface proteins (loss of Duffy antigen) as balanced polymorphisms in the context of malaria.

"Doctor, this will be a long war if for every division I have facing the enemy, I must count on a second division in hospital with malaria and a third division convalescing from this debilitating disease."

General Douglas MacArthur, May 1943 to Colonel Paul F. Russell, MC, the American army malaria consultant.
Destabilization Effect

- There are huge impacts of HIV/AIDS, malaria, and MTb on the critical infrastructures that sustain the security, stability, and viability of modern nation-states.

- In the developing world (esp Africa) these diseases undermine education and health systems, economic growth, micro enterprises, policing and military capabilities, political legitimacy, family structures, and overall social cohesion.

- Undermine the stability of already weakened states, adds to their vulnerability to extremists/terrorists who will seek to corrupt or coerce them into providing converts, cover, or cooperation.

- The real global war can be thought of being against these diseases - needs to be comprehensive, fought at many levels and on many fronts.
Recent Military History

- US / Somalia 1992-3 (233 cases; 77% *P. vivax*)
  - 30-75 cases/yr;
  - ~75% *P. vivax*
- US/ Afghanistan 2002 (38 cases)
- US / Liberia 2003 (80 cases)
- US/ Afghanistan today (>100 cases/yr)
- US/ Haiti 2010 (10 cases)
- Liberia 2009 (multiple cases, 1 death)
- Liberia 2010 (7 cases)
Joint Task Force Liberia 2003

- 225 Marines in Monrovia, Liberia < 2 weeks
  - Attack rate = 36% (80/225)
  - Evacuated to USA = 19% (43/225)
  - Severe = 2% (5/225)
    - 5 in intensive care unit
    - 4 on ventilators

- Prevention for military (travelers)
  - Difficult in operational areas
  - Requires consistent, reliable use of:
    - Mosquito repellants
    - Bed nets
    - Treated uniforms
    - Antimalarial drugs (drug-resistance, side-effect & compliance)

- Diagnostic / treatment delay = high risk severe disease

- Vaccine would be of great benefit

• Jesuit’s Bark, due to alkaloids, is the most celebrated specific remedy for all forms of malaria. It is obtained from several species of the genus cinchona, of the order Rubiaceae

• 1630: Countess Chinchon, the wife of Spanish Viceroy, was saved from terminal malaria by bark powders recommended by the Jesuits of Saint Paul’s College in Lima, Peru

• 1632: Jesuit Barnabe’ de Cobo (1582-1657) rendered important services in the exploration of Mexico and Peru. In his capacity of procurator of the Peruvian province of his order, he brought the bark from Lima to Spain, and afterwards to Rome and other parts of Italy
Plasmodium falciparum Becomes Resistant to Antimalarial Drugs
Continuous New Drug Development and Licensure is Required

<table>
<thead>
<tr>
<th>Drug</th>
<th>Introduced</th>
<th>First Reported Resistance</th>
<th>Difference (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinine</td>
<td>1632</td>
<td>1910</td>
<td>278</td>
</tr>
<tr>
<td><strong>Chloroquine</strong></td>
<td>1945</td>
<td>1957</td>
<td>12</td>
</tr>
<tr>
<td><strong>Proguanil</strong></td>
<td>1948</td>
<td>1949</td>
<td>1</td>
</tr>
<tr>
<td><strong>Sulfadoxine-pyrimethamine</strong></td>
<td>1967</td>
<td>1967</td>
<td>0</td>
</tr>
<tr>
<td><strong>Mefloquine</strong></td>
<td>1977</td>
<td>1982</td>
<td>5</td>
</tr>
<tr>
<td><strong>Malarone</strong></td>
<td>1997</td>
<td>2002</td>
<td>5</td>
</tr>
</tbody>
</table>

** WRAIR support for US FDA approval

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Multi-Drug Resistant Falciparum Malaria Means that Effective Drugs (ACTs) are not Affordable

In 1900; 53% land area malarious; 890,000,000 people at risk
In 2002; 27% land area malarious; 3,400,000,000 people at risk

*P. vivax*: chloroquine prophylactic or treatment failure
Malaria Development in Mosquitoes
From Red Cell to Red Cell and Again

**Action**
- Liver cell bursts
- Parasites escape

**Action**
- Invades RBC
- RBC swells
- RBC rigid
- RBC sticky knobs

**Action**
- Infected RBC sticks to blood vessel wall

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Anopheline Mosquitos

• 50->80 species capable of transmission
• <40 really important
• Female requires blood meals for egg broods
Anopheline Mosquitos

• Life cycle – 7 to 20 days (egg to adult)
  – egg -> larva -> pupa -> adult
  – Females mate once and lay 200-1000 eggs in 3-12 batches over a lifetime
  – Find their host by chemical and physical stimuli
  – Average life span of mosquito < 3 weeks

• Malaria development – 7 to 12 days
  – Each male & female gametocyte produce >10,000 sporozoites
VectorMap

Know the vector, know the threat

Welcome to VectorMap!

VectorMap is a product of the Walter Reed Biosystematics Unit based in the Smithsonian Institution. VectorMap provides disease maps, and mapped collection data and distribution models for arthropod disease vector species, including mosquitoes, ticks, sand flies, mites, and fleas, as well as the hosts/reservoirs of vector-borne disease pathogens. Collection records are searchable and downloadable, users can map and contribute their own georeferenced collection data or distribution models, and all contributions have full attribution. Currently, MosquitoMap has 314,443 records, TickMap has 96,158 records, and SandflyMap has 7,030 records. In addition, there are 8,399 flea records, as well as a small number of chigger mites, mite-borne scrub typhus, and host/serovar records.

WHAT'S NEW?>>>>>>Take the VECTORMAP SURVEY!<<<<<<VECTORMAP TUTORIAL

VectorMap is designed to preserve and make available the results of past collecting and distribution modeling activity, and to provide a unique resource for exploring possible disease risk factors. The utility of VectorMap will increase as more records and models are added. Contributions are encouraged, especially from individuals and organizations with digitized, georeferenced records and those involved in ongoing mosquito surveillance. VectorMap is modeled on MosquitoMap - see International Journal of Health Geographics. For an introduction to georeferencing standards and procedures see Journal of Medical Entomology.

MosquitoMap is useful for:
- informing decisions about where mosquito collection efforts should be directed
- identifying areas relevant to the study of mosquito biogeography, evolution and biodiversity
- allowing predictions about the potential spread of exotic mosquito introductions
- allowing predictions about the potential effects of global warming on mosquito distributions
- allowing insights into mosquito community structure, and environmental and climatic correlates to species occurrence (ecological niche)
- identifying mosquito-borne disease vectors
- identifying cryptic evolutionary lineages that differ in geographic or ecological space.

The Mal-area calculator

A novel enhancement of VectorMap is the Mal-area calculator (MAC) that quantifies the overlap between vector and pathogen distribution models, and host (human/population). The co-occurrence of vectors, parasites and hosts are required for many vector-borne diseases, and the MAC quantifies this co-occurrence for a given area, thus potentially providing a map and simple index of disease risk for any area of interest. At the moment the MAC is at the 'proof of concept' stage, but we plan to roll out an operational version in the near future!

VectorSurv

An associated application in preparation is VectorSurv, designed to host longitudinal survey data for arthropod vectors. Data from traps that are routinely monitored, often over many years, provides a valuable resource for assessing disease transmission risk, and for identifying the climatic and phenological factors responsible for temporal changes in abundance. VectorSurv is designed for online input and display of surveillance data.

For best performance, set screen resolution for 1024 x 768 or greater, and use IE 6.0 or greater, Firefox 2.5 or greater, or Safari 3 or greater.

By downloading and/or viewing data on the MosquitoMap, SandflyMap, and TickMap portals, you are agreeing to these conditions.

OPEN MosquitoMap

OPEN TickMap

OPEN SandflyMap
Malaria Parasites and Their Life Cycles

• Four human forms of malaria
  – *Plasmodium vivax*
    • 48h cycle, young RBCs, worldwide
  – *Plasmodium malariae*
    • 72h cycle, older RBCs, worldwide
  – *Plasmodium ovale*
    • 48h cycle, young RBCs, Africa
  – *Plasmodium falciparum*
    • 48h cycle, all RBCs, Tropical regions
# Prepatent & Incubation Periods
(parasites in blood vs. illness)

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>PREPATENT PERIOD</th>
<th>INCUBATION PERIOD</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. falciparum</em></td>
<td>11 - 14 days</td>
<td>8 - 15 days</td>
</tr>
<tr>
<td><em>P. vivax</em></td>
<td>11 - 15 days</td>
<td>12 - 20 days</td>
</tr>
<tr>
<td><em>P. ovale</em></td>
<td>14 - 26 days</td>
<td>11 - 16 days</td>
</tr>
<tr>
<td><em>P. malariae</em></td>
<td>21 - 28 days</td>
<td>18 - 40 days</td>
</tr>
</tbody>
</table>
Plasmodium knowlesi

- Simian species of malaria naturally infecting macaques in Southeast Asia
- Resembles human species by microscopy
  – *P. malariae* (affects any age cell like *P. falciparum*)
- 24 hour replication cycle
  – Can cause severe and fatal infections
- Large numbers of human cases reported initially from Malaysian Borneo
- Subsequent reports of human cases in Peninsular Malaysia, Singapore, and the Philippines
Diagnosis

• Gold standard – Giemsa thick & thin smears
  – Species and parasite density determined
  – Labor intensive, modest cost
  – False negative circumstances
    • Parasites not present in circulation
  – False positive circumstances
    • Parasites seen may not be the cause of fever in endemic areas (Kisumu example of misdiagnosis…)
  – In highly endemic areas, clinical diagnoses made
Plasmodium vivax
Plasmodium falciparum
Rapid Diagnostic Tests

• Currently acceptable test(s)
  – *Binax Now*, Inverness Medical Innovations, Inc.

• Reliability
  – False negatives – Prozone Effect
  – Hyperparasitemia – too much antigen
  – HRP-2 assays (16/17) most affected; pLDH and aldolase not affected

• Follow-up
  – FDA ‘clearance” Labeling – what does it actually say?
NOW® ICT Malaria (Binax, Inc., Portland ME)

- Less than 15 minutes
- Non-microscopic
- Single reagent
- Minimally-trained operator
- Environmentally robust
- RDTs will NOT replace malaria microscopy
  - Confirmatory test for species, parasite density
  - Back-up to rule out inaccurate results
Parasite Growth in the Blood

Log+ increase in parasites per 48-hour cycle (for *P. falciparum*)

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Parasitemia</th>
<th>Parasites/ml</th>
<th>Parasite burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expert Microscopy</td>
<td>0.0005%</td>
<td>20-50/ml</td>
<td>$10^8$ parasites</td>
</tr>
<tr>
<td>Symptoms in non-immunes</td>
<td>0.002%</td>
<td>100/ml</td>
<td>$10^9$ parasites</td>
</tr>
<tr>
<td>Malaria RDT</td>
<td>0.005%</td>
<td>100-1000/ml</td>
<td>$10^{9-10}$ parasites</td>
</tr>
<tr>
<td>Severe malaria</td>
<td>2%</td>
<td>100,000/ml</td>
<td>$10^{12}$ parasites</td>
</tr>
<tr>
<td>Death</td>
<td>10%</td>
<td>500,000/ml</td>
<td>$10^{13}$ parasites</td>
</tr>
</tbody>
</table>
“Good doctors are useless without good discipline. More than half the battle against disease is fought not by doctors, but by regimental officers. It is they who see that the daily dose of mepacrine is taken, that shorts are never worn, that shirts are put on and sleeves turned down before sunset. . . I therefore had surprise checks of whole units, every man being examined. If the overall result was less than 95% positive, I sacked the commanding officer. I only had to sack three; by then the rest had got my meaning.”

General Slim, Burma Campaign, WW II
(Under General Slim, the malaria rate in troops decreased from 12 per 1,000/day to 1 per 1,000/day)
Malaria Treatment
US ‘2014’

• Intravenous treatment of severe malaria
  – Quinidine gluconate
  – Treatment IND with IV Artesunate

• Oral treatment of uncomplicated *P. falciparum* malaria
  – Proguanil / atovaquone (Malarone®)
  – Artemether-lumefantrine (Coartem®)
  – Quinine sulfate + doxy or PS
  – Mefloquine (Lariam®)
  – Chloroquine (Aralen®)

• Available and can be used (Rx adjuncts)
  – Doxycycline, clindamycin, azithromycin

• Radical cure of relapsing malaria
  – Chloroquine + primaquine
CDC’s Compassionate Use IND

- WRAIR produced 1,000 vials of the “clinical lot” for compassionate use (another 10,000 vials being produced now – available in May 2010)
- CDC has a Compassionate Use IND for IV AS
  - Compassionate Use IND went into effect on 21 June, 2007
  - Complete cross-reference to U.S. Army IND for IV AS
  - Administered by Domestic Response Unit & Malaria Branch
  - Announcement Made on 03 August, 2007 in MMWR
- Now released to Canadians, and will be made available in Australia, EU, and elsewhere
Evidence of Artemisinin-Resistant Malaria in Western Cambodia

![Graph A](image1)

**Figure 1.** Parasite Density, Parasite-Clearance Time, and 50% Inhibitory Concentration (IC$_{50}$) among Patients Receiving Artesunate, According to Clinical Outcome.

Panel A shows the parasite-reduction curves for the 56 patients who were cured, the 2 patients classified as having artemisinin-resistant infections, and the 2 with drug failures (i.e., patients who had recrudescence but who were not classified as having artemisinin-resistant infection, since the drug level was inadequate). The data points and horizontal I bars denote the means and standard errors. Panel B shows the parasite-clearance times in the artemisinute group, as compared with the IC$_{50}$ for dihydroartemisinin (R=0.31, P=0.03). Orange circles indicate patients whose infection was classified as artemisinin-resistant, and blue squares patients in whom treatment failed but whose infection was not classified as resistant.
DRUG

Artemisinin
Atovaquone
Azithromycin
Chloroquine
Doxycycline
Fansidar
Halofantrine
Mefloquine
Primaquine
Proguanil
Quinidine gluconate
Quinine

PROBLEMS

Recrudescence, Neurotoxicity
Resistance
Limited efficacy
Resistance
Phototoxicity, GI intolerance
Resistance, Allergic Rxns
Cardiototoxicity
Resistance, Psychiatric effects
Narrow Therapeutic Index
Resistance, Mouth ulcers
Going off the market?
Resistance, Tinnitus
DoD Antimalarial Drug Program
The Biggest Little Drug Company in the World

- Filed 63 IND’s with US FDA
  - Chloroquine
  - Primaquine
  - C-P Tablets
  - Mefloquine
  - Doxycycline
  - Halofantrine
  - Fansidar
  - Malarone
  - IV Artesunate
Vaccines

Pre-erythrocytic

Transmission Blocking

Erythrocytic

MOSQUITOES

Oocyst

Sporozoites

Anopheles Female Mosquito

Gametocytes

Merozoites

Liver Schizonts

Sporozoites

Hyponozoite

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Approaches to Control

• Vector Control Methods
  – Breeding site control, larvicide, adulticide, bed nets and personal protection

• Treatment Strategies
  – Passive case finding and self-referral
  – Home treatment early in course of disease
  – Prophylaxis in selected groups
Controversies in Malaria

• Prophylaxis... drug to use?
  – Mefloquine vs. Malarone vs. Doxycycline

• Prophylaxis... to do or not?
  – Short-term vs. Long-term Deployments

• Prophylaxis... duration?
  – Continuous vs. Interrupted

• RDTs...
Malaria
Take Home Points

• Malaria continues to evolve, not just in resistance, but in new species
• Malaria is as important a consideration for force health protection today as ever
• Malaria is not just a force health protection issue, but a strategic stability operations consideration in the global war on terrorism
• We have more tools today than ever, but we can lose them at any time and we must understand and respect their limitations
Reality – Case study

- 45 y/o Male from Ivory Coast. Lived there 20 yrs ago and now owns property and visits every few years
- Last visit 2008 and took prophylaxis. Went this year from Feb to mid-Mar and had an uneventful stay but did not take prophylaxis
- Returned 15Mar and on the 24th or so got fevers/chills and rigors
- Used OTCs 1 day, had syncope while at work
- Civ ER via EMS on the 26th. Labs sig only for plts 60s and dx falciparum malaria by giemsa with 0.7% parasitemia
- Give him a script of oral quinine and doxy. He took doxy but was unable to fill oral quinine due to pharmacy avail (cost)
- On the 28th felt worse. Parasitemia now 0.5% and labs the same with plt 46 main abnml other than mild prerenal azotemia
- Response to malarone po first 24hr in ICU and d/c after 3rd day
- 14d of primaquine given due to overabundance of caution. Seen Monday and he was doing well
Fighting Malaria

• Requires expensive, sustained efforts
• Medical facilities are not equipped to quickly and accurately diagnose and effectively treat malaria
• Effective control efforts if subsidized and applied
  – Indoor Residual Spraying (IRS) with DDT - saves lives
  – Insecticide Treated Bed Nets (ITNs) - save lives
  – Artemisinin combinations treatment – saves lives
  – Improved diagnosis – use expensive drugs for those that need it
  – World is waiting for a malaria vaccine
• Eradication requires multiples efforts and multiple solutions
“Science is not an accessory occupation for man but an essential activity…”

Teilhard de Chardin
“The Phenomenon of Man”
QUESTIONS?

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