Malaria

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Slides courtesy of:
COL (Ret) Kent Kester
COL James Cummings
Malaria is a complex, large global problem

Current strategies are inadequate

DoD is making progress towards malaria solutions (drugs and vaccines)

Multi-pronged efforts are ongoing in the areas of malaria control, elimination, and eradication.
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**: May become chronic carriers (esp. *P. vivax*)
  - **ILL HEALTH, LEARNING DISABLED**

**RESERVOIRS OF INFECTION**
History

- Chinese writings (2700 BCE)
- The Eber’s papyrus (1550 BCE)
- 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 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
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)

Cumulative numbers of cases (x 1000)
Sprayed houses per 1000 population

Decreasing DDT use
Increasing malaria cases

Destabilization Effect

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

- In the developing world (esp sub-Saharan 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
# Malaria and Morbidity in the US Military

<table>
<thead>
<tr>
<th>Conflict/Deployment</th>
<th>Year</th>
<th>Morbidity and Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>WWII</td>
<td>1939–1945</td>
<td>600,000 cases mostly in Pacific theater. In some areas of South Pacific malaria rates were 4 cases per person per year</td>
</tr>
<tr>
<td>Korean War</td>
<td>1950–1953</td>
<td>Malaria rate 611/1000/year; 3000 cases in troops returning to US</td>
</tr>
<tr>
<td>Vietnam War</td>
<td>1962–1975</td>
<td>100,000 cases, Hospital admissions 27/1000/year 1970: 2222 cases (mostly <em>P. vivax</em>) treated in United States</td>
</tr>
<tr>
<td>Somalia</td>
<td>1992–1994</td>
<td>48 cases; 243 cases in forces on return home (<em>P. vivax</em>)</td>
</tr>
<tr>
<td>Nigeria</td>
<td>2001</td>
<td>Special forces 7/300 (2 deaths)</td>
</tr>
<tr>
<td>Afghanistan (OEF)</td>
<td>2001-</td>
<td>Over 400 cases since 2005</td>
</tr>
</tbody>
</table>

“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 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.*
Operational Impact - Liberia, 2003

- 80 of 220 (36%) Marines contracted falciparum malaria
- 46 required medical evacuation
- 5/80 (6.25%) were severe
  - Requiring ICU admissions
  - Four on ventilators
- Key problems:
  - Non-compliance
  - Inability to make the diagnosis
  - Cost- $1.2M
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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**Quinine**
- **Chloroquine**
- **Proguanil**
- **Fansidar**
- **Mefloquine**
- **Malarone**

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Multi-Drug Resistant Falciparum Malaria Means that Effective Drugs 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
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
Malaria Life Cycle

Key Point: most blood-stage schizonticides are suppressive—this is why prophylaxis is continued upon redeployment
Definitive host mosquito

Ingests 3 ul of blood with 100-300 gametes

Gametocytes viable for 28 days

Plasmodium Life Cycle

Clinical signs and symptoms in erythrocytic stages of ring, trophozoite, and schizont

28 days in mosquito

Oocysts on gut wall

100’s Sporozoites

Within hours invade 1-2 liver cells

48-72 hrs released 1,000’s Merozoites in liver for seven to 10 days. P. vivax & ovale hypnozoite for months.
Anopheline Mosquitoes

- 50->80 species capable of transmission
- <40 responsible for majority of transmission
- 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 Biosystems 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, sandflies, flies, and beetles, as well as the hosts/reservoirs of vector-borne disease pathogens. Collection records are searchable and downloadale, and can be mapped and contribute their own georeferenced collection data or distribution models, and all contributions have full attribution. Currently, MosquitoMap has 314,443 records, TickMap has 34,114 records, and SandflyMap has 17,986 records. In addition, there are 8,995 flea records, as well as a small number of other arthropods, ticks, sandflies, flies, and beetles.

VectorMap is designed to preserve and make available the results of past collecting and detection 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 georeferenced records and those interested in ongoing 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
- assembling mosquito community structure, and environmental and climatic correlates to species occurrence (exposure risk)
- allowing customized rather than just local studies of vector-borne disease
- identifying cryptic evolutionary lineages that differ in geographic or ecological space.

The weighted calculator

A novel enhancement of VectorMap is the weighted calculator (WAC) that investigates 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 WAC 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 WAC is at the 'proof of concept' stage, but we plan to roll out an operational version in the near future.

VectorSurf

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

For best performance, use 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.

Thank you and completeness of data cannot be guaranteed. Users assess these data at their own risk.

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

OPEN MosquitoMap
OPEN TickMap
OPEN SandflyMap

http://www.vectormap.org/

7/23/2013
Malaria Parasites and Their Life Cycles

- **Four (5) human forms of malaria**
  - *Plasmodium vivax* (benign “tertian”)  
    - 48h cycle, young RBCs (reticulocytes), worldwide
  - *Plasmodium malariae* (“quartan”)  
    - 72h cycle, older RBCs, worldwide
  - *Plasmodium ovale* (“ovale tertian”)  
    - 48h cycle, young RBCs, Africa
  - *Plasmodium falciparum* (“malignant tertian”)  
    - 24-48h cycle, all RBCs, Tropical regions
  - *Plasmodium knowlesi*  
    - 24h cycle, probably all RBC’s, Southeast Asia (Malaysia/Indonesia/Borneo)
## Prepatent & Incubation Periods
(parasites in detectable 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>
<tr>
<td><em>P. knowlesi</em></td>
<td>11 days?</td>
<td>10-12 days?</td>
</tr>
</tbody>
</table>
Comparison of Malaria Fever Curves

Adapted from Thayer and Hewetson
Johns Hopkins Hosp Reports V 1895 p. 3-224

“Tertian” *P. vivax*

“Quartan” *P. malariae*

“Aestivo-autumnal “Quotidian” *P. falciparum*
The Malaria Rigor

Pyrogenic density is parasite density at time of fever.

*P. vivax* pyrogenic density is 100 parasites/μl

*P. falciparum* pyrogenic density ranges from 0 to 10,000/μl in nonimmunes

Semi-immune can have up to 100,000 par/μl without fever.
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
Clinical Complications of Malaria

- **P. falciparum**
  - Cerebral coma
  - Anemia
  - Pulmonary Edema
  - Renal Failure
  - Shock
  - Lactic acidosis
  - Hypoglycemia
  - Tropical splenomegaly
    - Skin ulceration
  - Pregnancy
    - Maternal death
    - Stillbirth
    - Low birth weight
    - Anemia

- **P. vivax (ovale)**
  - Splenic rupture
  - Anemia (mild)
  - Debilitating fever
  - Higher TNF-α per parasite

- **P. malariae**
  - Immune complex
  - Glomerulonephritis → nephrotic syndrome
Malaria Complications

Nephrosis/Edema

Tropical splenomegaly
(Hyperreactive Malarial Syndrome)
Diagnosis

- **Gold standard – Giemsa thick & thin smears**
  - Species and parasite density determined
  - Labor intensive, modest cost
  - False negative circumstances
    - Parasites not present in circulation (“Sequestration”): *P. falciparum*

- False positive circumstances
  - Parasites seen may not be the cause of fever in endemic areas – bacteremia (prominently Salmonella sp.) common

- 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? (need for microscopy confirmation)
NOW® ICT Malaria (Binax, Inc.)

- 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/ul</th>
<th>Parasite burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expert Microscopy</td>
<td>0.0005%</td>
<td>20-50</td>
<td>$10^8$ parasites</td>
</tr>
<tr>
<td>Symptoms in non-immunes</td>
<td>0.002%</td>
<td>100</td>
<td>$10^9$ parasites</td>
</tr>
<tr>
<td>Malaria RDT</td>
<td>0.005%</td>
<td>100-1000</td>
<td>$10^{9-10}$ parasites</td>
</tr>
<tr>
<td>Severe malaria</td>
<td>2%</td>
<td>100,000</td>
<td>$10^{12}$ parasites</td>
</tr>
<tr>
<td>Death</td>
<td>10%</td>
<td>500,000</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)
Treatment Algorithm (TG336)

Patient ill with fever > 101 °F and is/has been in a malarious area.

YES

MUST rule out malaria. Start empiric treatment if malaria is suspected. Consider rapid medical evacuation.

YES

Perform blood smears or rapid diagnostic test (RDT). If initial smear or RDT is negative, repeat in 8-12 hours. If still negative, repeat a third time 8-12 hours later. [Only after three properly spaced diagnostic tests should one exclude a diagnosis of malaria.] Negative tests that are clinically considered possible false-negative should be treated even as testing continues. If accurate and reliable diagnostic testing is not available within 1-2 hours OR if clinical symptoms worsen during serial testing and no alternative diagnosis has been confirmed, empiric treatment for chloroquine-resistant falciparum malaria is recommended.

YES

If smear or RDT positive, treat (see Treatment section). Report confirmed and empirically treated cases to preventive medicine authorities.

Particularly non-Pf
Malaria Treatment (Adult doses)

- **Intravenous treatment of severe malaria**
  - Quinidine gluconate:
    - Load with 10 mg/kg in 250 cc over 1-2 hours
    - Maintenance dose of 0.2 mg/kg/min for 72 hours
  - Artesunate (treatment IND): 2.4 mg/kg at 0, 12, 24, 48, and 72 hours

- **Oral treatment of uncomplicated* P. falciparum* malaria**
  - Proguanil / atovaquone (Malarone®): 4 tabs daily for 3 days
  - **Artemether-lumefantrine (Coartem®):**
    - 4 tabs x 1, followed by 4 tabs at 8 hours, then 4 tabs twice daily for 2 days (6 total doses)
  - Quinine sulfate + doxy or PS
  - Mefloquine (Lariam®): 1250 mg (5 tabs) x 1
  - Chloroquine (Aralen®): **(DO NOT USE IN AFRICA OR ASIA)**
    - 1 gram (600 mg base) loading dose
    - 500 mg (300 mg base) in 8 hours, 24 hours, and 48 hours

- **Available and can be used (Rx adjuncts)**
  - Doxycycline, clindamycin, azithromycin

- **Radical cure of relapsing malaria**
  - Chloroquine + primaquine

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*CDC Health Information for International Travel 2014*
Oral vs. Intravenous Treatment

- Parasitemia >5%
- Unable to tolerate oral medications
- Signs of end-organ damage
  - Renal failure
  - Pulmonary edema/respiratory failure
  - Coma
  - Severe anemia (transfusion)

If yes to any of the above, then IV
CDC’s Compassionate Use IND

- WRAIR produced 1,000 vials of the “clinical lot” for compassionate use IV Artesunate (AS)
- 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
  - Forward supply located at LRMC
<table>
<thead>
<tr>
<th><strong>DRUG</strong></th>
<th><strong>PROBLEMS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemisinin</td>
<td>Recrudescence, Neurotoxicity</td>
</tr>
<tr>
<td>Atovaquone</td>
<td>Resistance</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Limited efficacy</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Resistance</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Phototoxicity, GI intolerance</td>
</tr>
<tr>
<td>Fansidar</td>
<td>Resistance, Allergic Rxns</td>
</tr>
<tr>
<td>Halofantrine</td>
<td>Cardiotoxicity</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>Resistance, Psychiatric effects</td>
</tr>
<tr>
<td>Primaquine</td>
<td>Narrow Therapeutic Index</td>
</tr>
<tr>
<td>Proguanil</td>
<td>Resistance, Mouth ulcers</td>
</tr>
<tr>
<td>Quinidine gluconate</td>
<td>Going off the market?</td>
</tr>
<tr>
<td>Quinine</td>
<td>Resistance, Tinnitus</td>
</tr>
</tbody>
</table>
Evidence of Artemisinin-Resistant Malaria in Western Cambodia

Figure 1. Parasite Density, Parasite-Clearance Time, and 50% Inhibitory Concentration (IC₅₀) 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 artesunate group, as compared with the IC₅₀ 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.

NEJM 359;24 11Dec08 2619
Prophylaxis

- Malarone
- Doxycycline
- Mefloquine-if you can’t tolerate the first 2 and not in SE Asia
- Chloroquine-few areas where Pf is sensitive
- Primaquine-short duration

Table 1. Relative Risk of Malaria among Travelers, 2000 through 2002.*

<table>
<thead>
<tr>
<th>Region Visited</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very-low-risk area †</td>
<td>1.0</td>
</tr>
<tr>
<td>Caribbean</td>
<td>3.8 (1.9–7.5)</td>
</tr>
<tr>
<td>North Africa</td>
<td>6.9 (3.6–13.3)</td>
</tr>
<tr>
<td>South America</td>
<td>8.3 (4.9–13.9)</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>11.5 (8.3–15.9)</td>
</tr>
<tr>
<td>Central America</td>
<td>37.8 (24.0–59.6)</td>
</tr>
<tr>
<td>South Asia</td>
<td>53.8 (37.4–77.4)</td>
</tr>
<tr>
<td>Oceania</td>
<td>76.7 (50.8–115.9)</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>207.6 (164.7–261.8)</td>
</tr>
</tbody>
</table>

* Approximate relative risks were based on 1140 cases of malaria among travelers in the GeoSentinel database, with areas visited as numerators and tourist arrivals in that region (according to World Tourism Organization data) as estimates for denominators. Adapted from Leder et al.†2
† Very-low-risk areas were Europe, Northeast Asia, Australia, New Zealand, North America, and the Middle East.
## Chemoprophylaxis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tablet Size</th>
<th>Dose</th>
<th>Start (pre-deploy)</th>
<th>Stop (re-deploy)</th>
<th>Disadvantages</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malarone (Atovaquone/Proguanil)</td>
<td>250mg/100mg</td>
<td>One tablet daily</td>
<td>1-2 days</td>
<td>7 days</td>
<td>Expensive, no if Cr Cl &lt;30 ml/min, must be taken with food</td>
<td>No</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100mg</td>
<td>100mg daily</td>
<td>1-2 days</td>
<td>4 weeks</td>
<td>Photosensitivity, gastritis/esophagitis (must give with liquid, full stomach, upright for 30 minutes), vaginitis</td>
<td>No</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>250mg</td>
<td>250mg weekly</td>
<td>3 wks preferable, 1-2 OK</td>
<td>4 weeks</td>
<td>Resistance in SE Asia, Black box for depression/neurotoxicity, cardiac conduction abnormalities</td>
<td>Yes</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>500mg (300mg base)</td>
<td>500mg weekly</td>
<td>1 week</td>
<td>4 weeks</td>
<td>Resistance, pruritus in dark-skinned persons, rare blood dyscrasias, psoriasis, hx of psychosis, prolonged QT, rare retinopathy</td>
<td>Yes</td>
</tr>
<tr>
<td>Primaquine</td>
<td>26.3mg (15mg base)</td>
<td>30mg base</td>
<td>1 day</td>
<td>7 days</td>
<td>G6PD, food (gastric irritation), methemoglobinemia</td>
<td>No</td>
</tr>
<tr>
<td>Primaquine</td>
<td>26.3mg (15mg base)</td>
<td>30mg base</td>
<td>Protection against late relapse Pv/Po</td>
<td>Total of 14 days (6mg/kg total dose)</td>
<td>G6PD, food (gastric irritation), methemoglobinemia</td>
<td>No</td>
</tr>
</tbody>
</table>

Adapted from Freedman D, NEJM 2008
Controversies in Malaria

- **Prophylaxis... drug to use?**
  - Mefloquine (probably not) 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
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
QUESTIONS?

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