Overview of Malaria

Roger Bedimo, MD, MS
VA North Texas Health Care System
UT Southwestern Medical Center
Burden of Disease: Malaria

- Over 40% of the world’s population live in endemic areas
- Estimated 500 million clinical cases and 1-2 million deaths/year
- 3rd most common cause of death due to a communicable agent
In the 20th century, the boundary of malaria transmission was progressively rolled back from the north.
Burden of Malaria in Africa

- One African child dies of malaria every 30 seconds
- Higher in poor and rural areas
- In all malaria-endemic countries in Africa, malaria accounts for 25-40% of outpatient visits and 20-50% of hospital admissions

Although adults also become infected with malaria, the illness is usually less severe thanks to their acquired immunity. Infections in young children are serious and may kill if not treated promptly.

Source: WHO Global Burden of Disease project, estimates for 2000, reference 17

Figure 1.3
What is Malaria?

- A disease caused by infection with *Plasmodium* spp. parasites
- Carried from person to person by anopheline mosquitoes
- Six species of *Plasmodium* cause malaria
  - *P. vivax*, *P. falciparum*, *P. malariae* *P. ovale curtisii*, *P. ovale wallikeri*, *P. knowlesii*
  - *P. falciparum* causes most morbidity and mortality
- Symptoms include fever, nausea, vomiting, diarrhoea, tissue damage, multiple organ failure, severe anaemia, coma (cerebral Malaria), death
Global Distribution of *P. falciparum* and *P. vivax*
Estimating risk of infection, disease, and death

- ~ 50 billion infections with malaria parasites each year in Africa
- ~ 1:100 infections leads to clinical illness = 500 million cases of malaria each year
- ~ 1:50 cases of malaria results in the severe form of disease = 10 million cases of severe malaria each year
- ~ 1:5 cases of severe malaria leads to death = 1-2 million deaths due to malaria each year
What is Malaria?

- In regions of high malaria transmission, every member of the community might be chronically infected.

Percent positive parasitemia 13-24% even in seasons without transmission; Most patients asymptomatic.

Determinants of Malaria

Parasite → Environment → Host → Vector
Determinants of Malaria

Environment
Prevalence and Intensity of Parasitic Infections

Amebiasis
W. Africa

Malaria
Nigeria

Ascariasis
Iran

Age-Prevalence and Age-Intensity Curves
• In a stable malaria situation an equilibrium exists
• This may, however, include strong seasonality

Determinants of Malaria

Transmission

• Holoendemic
• Hyperendemic
• Mesoendemic
• Hypoendemic
• No Malaria

Immunity
Outcomes of Malarial Infestation

- Asymptomatic parasitemia (could be majority of population in some endemic areas)
- Simple malarial fever (2-3 episodes/child/year in endemic areas)
- Severe malaria (~1% of cases)
  - Severe malarial anemia
  - Cerebral malaria
  - Respiratory Distress and Others
- Death
Malaria: Prognostic Factors

<table>
<thead>
<tr>
<th>Parasite factors</th>
<th>Host factors</th>
<th>Geographic and social factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug resistance</td>
<td>Immunity</td>
<td>Access to treatment</td>
</tr>
<tr>
<td>Multiplication rate</td>
<td>Proinflammatory cytokines</td>
<td>Cultural and economic factors</td>
</tr>
<tr>
<td>Invasion pathways</td>
<td>Genetics (sickle cell trait, thalassaemia, ovalocytosis, Gerbich RBC, CD36, TNF-α, ICAM-1, CR1, MHC locus)</td>
<td>Political stability</td>
</tr>
<tr>
<td>Cytosadhherence</td>
<td></td>
<td>Transmission intensity</td>
</tr>
<tr>
<td>Rosetting</td>
<td>Age (no cerebral malaria in infants)</td>
<td>(Anopheles spp., seasonality of transmission, infectious bites per year, epidemics)</td>
</tr>
<tr>
<td>Antigenic polymorphism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antigenic variation (PfEMP1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaria toxin</td>
<td>Pregnancy</td>
<td></td>
</tr>
</tbody>
</table>

Clinical outcome

- Asymptomatic infection
- Fever (asymptomatic infection)
- Severe malaria (metabolic acidosis, severe anaemia, cerebral malaria)
- Death

Plasmodium Life Cycle

Mosquito Stages:
1. Oocyst
2. Release of sporozoites
3. Ruptured oocyst
4. Mosquito takes a blood meal (injects sporozoites)

Sporogonic Cycle:
5. Exflagellated microgametocyte
6. Microgamete entering macrogamete
7. Macrogametocyte

Human Liver Stages:
8. Ookinete
9. Ruptured oocyst
10. Release of sporozoites

Exo-erythrocytic Cycle:
11. Mosquito takes a blood meal (ingests gametocytes)

Human Blood Stages:
12. Immature trophozoite (ring stage)
13. Mature trophozoite
14. Ruptured schizont
15. Schizont
16. Gametocytes
17. Exflagellated microgametocyte
18. Microgamete entering macrogamete

CDC:
http://www.dpd.cdc.gov/dpdx
Clinical Presentation

- **Sporogonic cycle**
- **Infective Period**
- **Mosquito bites gametocytemic person**
- **Mosquito bites uninfected person**
- **Prepatent Period**
- **Incubation Period**
- **Parasites visible**
- **Symptom onset**
- **Clinical Illness**
- **Recovery**
Uncomplicated Malaria Symptoms

- “Classic” attack (rarely observed – lasts 6-10 hours)
  - Cold stage (patient feels cold, shivering)
  - Hot stage (fever, headache, vomiting, seizures in young children)
  - Sweating stage (sweat, then return to normal temp)
- Common symptoms
  - Fever, chills, sweats, headache, nausea & vomiting, body aches, and general malaise
    - If in non endemic region, these symptoms could be confused for other diseases
    - If in endemic region, may believe it is malaria without checking other causes
CLINICAL SIGNS & SYMPTOMS OF MALARIA

- Fever
- Chills
- Sweating

The hot stage

The sweating stage

The cold stage
## Disease Severity and Duration

<table>
<thead>
<tr>
<th></th>
<th>vivax</th>
<th>ovale</th>
<th>malariae</th>
<th>falciparum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of Initial</td>
<td>moderate to</td>
<td>mild</td>
<td>mild to</td>
<td>severe</td>
</tr>
<tr>
<td>Paroxysms</td>
<td>severe</td>
<td></td>
<td>moderate</td>
<td></td>
</tr>
<tr>
<td>Average Parasitemia</td>
<td>20,000</td>
<td>9,000</td>
<td>6,000</td>
<td>50,000-500,000</td>
</tr>
<tr>
<td>(per mm$^3$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum Parasitemia</td>
<td>50,000</td>
<td>30,000</td>
<td>20,000</td>
<td>2,500,000</td>
</tr>
<tr>
<td>(per mm$^3$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom Duration</td>
<td>3-8+ weeks</td>
<td>2-3 weeks</td>
<td>3-24 weeks</td>
<td>2-3 weeks</td>
</tr>
<tr>
<td>(untreated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum Infection</td>
<td>5-8 years*</td>
<td>12-20 months*</td>
<td>20-50+ years</td>
<td>6-17 months</td>
</tr>
<tr>
<td>Duration (untreated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+++++</td>
</tr>
<tr>
<td>Other Complications</td>
<td></td>
<td>renal</td>
<td>cerebral</td>
<td></td>
</tr>
<tr>
<td><em>Includes relapses from the hypnozoite stage.</em></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Peculiarities of *P. falciparum* malaria

- Clinical: High “Virulence”: Cerebral Malaria (CM)
  - Diffuse, potentially rapidly reversible encephalopathy with altered consciousness (confusion → coma) +/- seizures.
  - Unarousable Coma + evidence of *P. falc* infection + No other identifiable cause for coma (WHO Case Definition)
FIG. 6. Erythrocyte from in vitro culture, showing a late trophozoite of Plasmodium falciparum intracellularly and exhibiting knobs on the surface (arrows). Electron Micrograph, X45,600. (From Sun T. Pathology and Clinical Features of Protozoal Diseases. New York: Masson, 1982, with permission.)
Cytoadherence and rosetting in postcapillary vasculature.

# Indications of Severe Malaria and Poor Prognosis

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>cerebral malaria</td>
<td>unrousable coma not attributable to any other cause</td>
</tr>
<tr>
<td>severe anemia</td>
<td>hematocrit &lt;15% or hemoglobin &lt;50 g/l in the presence of parasite count &gt;10 000/µl</td>
</tr>
<tr>
<td>respiratory distress</td>
<td>defined by labored breathing and pulmonary edema that can progress to an acute respiratory distress syndrome</td>
</tr>
<tr>
<td>renal failure</td>
<td>low urine output and high serum creatinine despite adequate volume repletion</td>
</tr>
<tr>
<td>circulatory collapse (shock)</td>
<td>systolic blood pressure &lt;70 mm Hg in patients with cold clammy skin</td>
</tr>
<tr>
<td>acidemia/acidosis</td>
<td>arterial pH &lt;7.25 or plasma bicarbonate &lt;15 mmol/l</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td>whole blood glucose concentration &lt;2.2 mmol/l (&lt;40 mg/dl)</td>
</tr>
<tr>
<td>impaired consciousness</td>
<td>impaired consciousness less marked than unrousable coma, can localize a painful stimulus</td>
</tr>
<tr>
<td>repeated generalized convulsions</td>
<td>≥ 3 convulsions observed within 24 hours</td>
</tr>
</tbody>
</table>
### Indications of Severe Malaria and Poor Prognosis

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<tr>
<th>Manifestation</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>prostration or weakness</td>
<td>patient unable to sit or walk, with no other obvious neurological explanation</td>
</tr>
<tr>
<td>abnormal bleeding and/or coagulation</td>
<td>spontaneous bleeding from gums, nose, gastrointestinal tract, or laboratory evidence of disseminated intravascular coagulation</td>
</tr>
<tr>
<td>malarial hemoglobinuria</td>
<td>need to exclude hemoglobinuria due to antimalarial medications and to G6PD deficiency</td>
</tr>
<tr>
<td>jaundice</td>
<td>bilirubin &gt;43 μmol/l (&gt; 2.5 mg/dl)</td>
</tr>
<tr>
<td>hyperparasitemia</td>
<td>&gt;5% parasitized erythrocytes or &gt;250 000 parasites/μl (interpreted in light of immune status and prior exposure)</td>
</tr>
<tr>
<td>hyperpyrexia</td>
<td>core body temperature &gt;40°C</td>
</tr>
</tbody>
</table>
Plasmodium Life Cycle

Mosquito Stages:
1. Infective stage
2. Diagnostic stage
3. Ruptured oocyst
4. Release of sporozoites
5. Mosquito takes a blood meal (injects sporozoites)
6. Oocyst
7. Ookinete
8. Macrogametocyte
9. Microgametocyte
10. Exflagellated microgametocyte
11. Release of sporozoites

Human Liver Stages:
A. Liver cell
B. Infected liver cell

Exo-erythrocytic Cycle:
1. Mosquito takes a blood meal (injects sporozoites)
2. Ruptured schizont
3. Schizont
4. Exo-erythrocytic cycle

Sporogonic Cycle:
5. Human liver stages
6. Mature trophozoite
7. Exflagellated microgametocyte
8. Macrogametocyte
9. Microgametocyte
10. Ookinete
11. Oocyst

Erythrocytic Cycle:
- P. falciparum
- P. vivax
- P. ovale
- P. malariae
- Immature trophozoite (ring stage)
- Mature trophozoite
- Ruptured schizont
- Schizont
- Gametocytes
- Microgametocyte
- Exflagellated microgametocyte
- Macrogametocyte
- Ookinete
- Oocyst
Major Challenges of Malaria Life Cycle

- Hepatocyte Invasion
- Erythrocyte Invasion
  - Erythrocyte membrane receptors
- Intra-erythrocyte Survival
  - Parasite membrane generation; parasitophorous vacuole; parasite-derived molecules on erythrocyte membrane: cytoadherence
  - Large hemoglobin consumption; detoxification
- Immune Evasion
- Cytoadherence
Malaria Species: Microscopy

Ring-form trophozoites of *P. falciparum* in a thin blood smear.

Ring-form trophozoites of *P. vivax* in a thin blood smear.

Trophozoites of *P. ovale* in a thin blood smear.

Band-form trophozoites of *P. malariae* in a thin blood smear.

Schizont and ring-form trophozoite of *P. knowlesi* in a thin blood smear.
Pitfalls of Malaria Treatment in Endemic Areas

- Every fever is considered malaria and treated as such.
- Counterfeit drugs are abundantly available
- Drug resistance:
  - P. falciparum:
    - virtually all malaria-endemic areas have chloroquine resistance
    - Less widespread for other antimalarials:
  - P. vivax:
    - Identified in Papua New Guinea, spread to South East Asia, Indian Subcontinent, South America
History of travel to malaria-endemic area or clinical suspicion of malaria

Perform thick and thin blood films and read within a few hours

Blood film positive?

No

Repeat blood films every 12 to 24 h for a total of 3 sets

No

Blood film positive?

Yes

Calculate parasitemia

Evaluate clinical status and disease severity

Consider alternate diagnoses
Primaquine if not G6PD deficient

Admit to monitor for progression to severe disease

Admit to ICU; cardiac monitoring
<table>
<thead>
<tr>
<th>Drug</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atovaquine/Proguanil (Malarone)</td>
<td>-Star 1-2 days pre-trip; Stop 7 days post-return</td>
<td>-Contra-indications: pregnant and lactating women and children &lt;5Kg; renal impairment</td>
</tr>
<tr>
<td>250 mg/100 mg QD</td>
<td></td>
<td>-Cost</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>-OK for pregnant women</td>
<td>-Limited applicability (areas without CQ or Mefloquine resistance)</td>
</tr>
<tr>
<td>300 mg Q Week</td>
<td></td>
<td>-Star 1-2 weeks pre-trip; Stop 4 weeks post-return</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>-Least expensive</td>
<td>-Photosensitivity</td>
</tr>
<tr>
<td>100 mg QD</td>
<td>-Star 1-2 days pre-trip; Stop 7 days post-return</td>
<td>--Contra-indications: pregnant women and children &lt;8 years</td>
</tr>
<tr>
<td></td>
<td>-Can prevent other infections (rickettsiosis and leptospirosis)</td>
<td></td>
</tr>
</tbody>
</table>
# Chemoprophylaxis for Travelers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mefloquine 250 mg Q Week</td>
<td>-OK for pregnant women</td>
<td>-Avoid in areas with mefloquine resistance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Avoid in patients with seizure d/o &amp; certain psychiatric illnesses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Star 2-3 weeks pre-trip; Stop 4 weeks post-return</td>
</tr>
<tr>
<td>Primaquine QD</td>
<td>-Most effective medicine for preventing <em>P. vivax</em> and so it is a good choice</td>
<td>-Contra-indicated in patients with glucose-6-phosphatase dehydrogenase (G6PD)</td>
</tr>
<tr>
<td></td>
<td>for travel to places with &gt; 90% <em>P. vivax</em></td>
<td>deficiency</td>
</tr>
<tr>
<td></td>
<td>-Star 1-2 days pre-trip; Stop 7 days post-return</td>
<td>-Contra-indicated in pregnant women</td>
</tr>
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Available tools for the control and elimination of malaria

1. Effective case management (ACT)
2. Insecticide treated bednets (ITNs)
3. Vector control
4. Chemoprevention
5. Vaccine
Effective case management in the era of ACTs

- ACT’s have now become the standard of care throughout the world
  - Artesunate+mefloquine
  - Artemether-lumefantrine
  - Artesunate+amodiaquine
  - Dihydroartemisinin-piperaquine
- Excellent efficacy unless resistance to partner drug
  - Early reports of artemisinin resistance in Thai-Cambodia border
- May decrease transmission through anti-gametocyte effects
- Concern about drug availability and cost
Effective case management
Issues in resource poor settings

- Government recommends one first-line therapy for the whole country
  - Policy based on clinical surveillance studies
  - Drug subsidized for the public sector
  - ACTs currently too expensive in the private sector
- Most fevers are treated empirically as malaria at home
  - Urgent need to promote rationale use of ACTs
Insecticide Treated Bednets (ITN)

- Several randomized trials in a range of endemic settings have documented the efficacy of ITNs
  - Interventions done at the population level
  - ~10 fold reduction in transmission
  - ~2 fold decrease in incidence of clinical malaria
  - ~20% reduction in all cause childhood mortality
- One of the most cost effective interventions available
  - Bednets cost only a few dollars
- Long lasting ITNs
  - Insecticide impregnated into nets
  - Last 5 years
- Remaining issues: coverage and distribution
Insecticide Treated Bednets (ITN) Survey of 40 African Countries

- ↑ in ITN coverage (Children <5 y)
  - 1·7 M (1·8%) in 2000 → 20·3 M (18·5%) in 2007
  - 89·6 M children still unprotected; 30 M of them living in some of the poorest areas of Africa: 54% were living in only seven countries (Nigeria, DRC, Uganda, Sudan, Mozambique, Côte d’Ivoire, and Cameroon) and 25% in Nigeria alone.

- Overall, 33 (83%) countries have ITN coverage of less than 40% in 2007.

- Greater increase in ITN coverage in areas where free distribution had operated between survey periods.

Noor et al., Lancet 2009; 373(9657): 58-67
Vector control

- **Primary tool indoor residual spraying (IRS)**
  - Very effective in low transmission areas
  - Starting to be used in higher transmission settings in Africa
  - Limited data on what is the best insecticide and how often to spray
  - Very expensive

- **Other vector control measures**
  - Larvicide
  - Genetically modified mosquitoes
Chemoprevention

- Two main strategies
  - Chemoprophylaxis
  - Intermittent preventative therapy

- Target groups
  - Pregnant women
  - HIV infected patients
    - Daily trimethoprim-sulfamethoxazole
  - Infants and young children
    - Active area of research
Control of Malaria in Africa: Vaccines

- 1973 vaccine made from whole malaria parasites killed by irradiation could protect healthy persons from infection
  - Not a viable option for large scale production
- Decades of research failed to develop an effective vaccine
  - Limited understanding of immune correlates of protection
  - Organism extremely diverse and complicated
- Recent vaccine trials
  - RTS,S vaccine
    - Surface protein found in form of parasite injected by mosquitoes conjugated to Hep B surface Ag
    - Pilot study in 360 Gambian men: 34% efficacy in protecting against malaria infection but waned to 0% by 15 weeks
    - 1500 children in Mozambique: 30% reduction in clinical malaria and 58% reduction in severe malaria after 6 months
RTS,S: Phase III Study

- Conducted in 11 sites located in 7 countries in sub-Saharan Africa:
- 15,460 children in two groups:
  - 6-12 weeks
  - 5-17 months
- Primary endpoint: Efficacy against clinical malaria in the 12 months post-vaccination in first 6000 children 5 to 7 months
- Secondary endpoint: severe malaria
Cumulative Incidence of Malaria

- Incidence of malaria: 0.32 vs. 0.55 episodes/person-year
- Per-protocol vaccine efficacy overall 55.8%
- Vaccine efficacy not constant over time
- Higher vaccine efficacy earlier in follow-up period
- 34.8% protection against severe malaria
- No mortality benefit
Future Considerations

- Full results expected 2014
- Potential vaccine licensure 2015
- Is this the right vaccine?
  - Is 50% efficacy enough
  - Single antigen vs. multiple antigen
  - Duration of protection, effect on premunition
  - *P. falciparum* only
- Diversion of resources