

1. Malaria and Babesia

Malaria and Babesia

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Diseases

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2. Apicomplexans:

Apicomplexans:

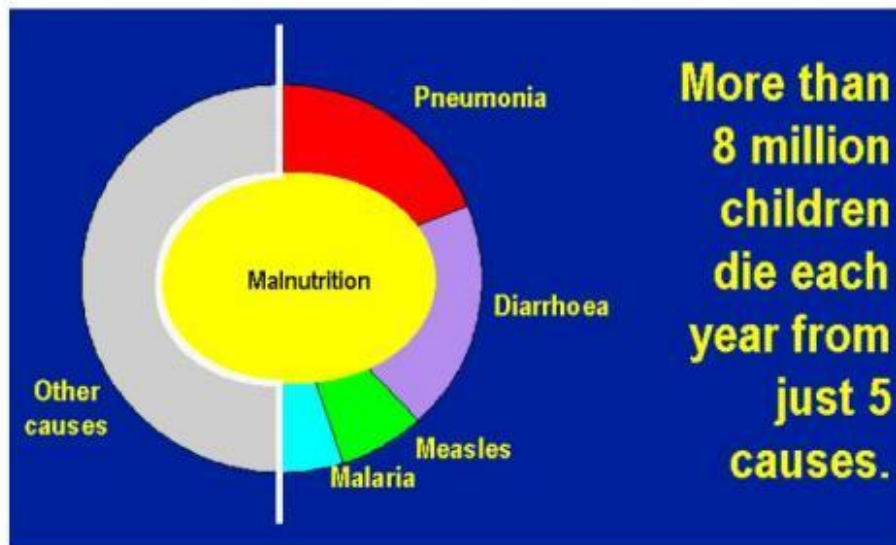
- ✦ So named because of the presence of an “apical complex” consisting of
 - ◆ **Rhoptries**
 - ◆ **Micronemes**
 - ◆ **Dense granules**

- ✦ During invasion function in:
 - Zoite motility**
 - Attachment to host cells**
 - Invasion into cells**
 - Establishment of the parasitophorous vacuole**

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3. Malaria: Major Causes of Childhood Deaths

Major Causes of Childhood Deaths



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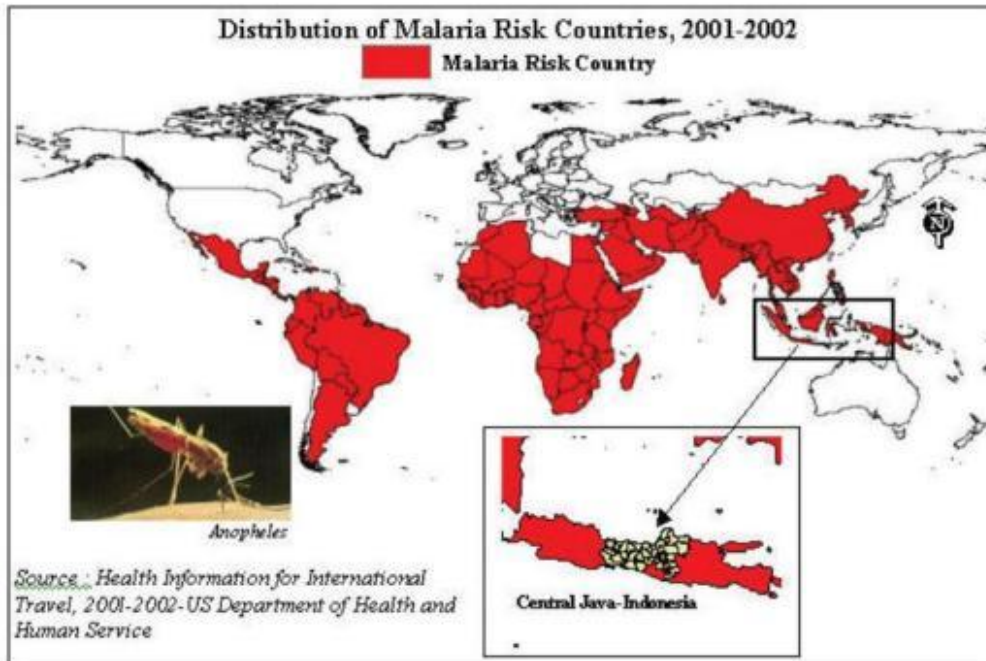
4. Current Worldwide status of Malaria

Current Worldwide status of Malaria

- ☞ 300 to 500 million cases occur each year
- ☞ *Plasmodium falciparum* is responsible for 1-2 million deaths yearly
 - A death from malaria occurs every 30 seconds
 - 90% of deaths occur in sub-Saharan Africa
 - Most deaths occur in children < 5 years old
- ☞ Number of malaria cases is increasing since the failure of the global malaria eradication campaign in the late sixties
- ☞ Drug-resistant parasites are widespread
- ☞ Insecticide-resistant mosquitoes are common

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5. Malaria: Distribution of Malaria Risk Countries, 2001-2002...



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6. Causes of Human Malaria

Causes of Human Malaria

- ☞ *Plasmodium falciparum*
 - Occurs worldwide
 - Responsible for greatest morbidity + mortality
- ☞ *P. vivax*
 - Occurs in Latin America, Asia, Middle East, North and East Africa
- ☞ *P. ovale*
 - Only found in Central-West Africa (very similar to *P. vivax*)
- ☞ *P. malariae*
 - Occurs in low levels where ever malaria is endemic

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7. Modes of Transmission

Modes of Transmission

- ☞ Bite of female *Anopheles* mosquito
 - Most common mode of transmission

- ☞ Transfusion of infected erythrocytes

- ☞ Maternal-fetal

- ☞ Inoculation from a contaminated needle

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8. Malaria: Species differences

Species differences:

Differences in duration of the lifecycle stages, number of merozoites per schizont, size of tissue schizont

Periodicity of febrile attacks and duration of fever

Erythrocyte preference: *P. falciparum* attacks all RBCs; *P. vivax* and *P. ovale* prefer reticulocytes; *P. malariae* older erythrocytes.

P. ovale and *P. vivax* infections: infected parasites can harbor dormant parasites (hypnozoites)-can cause relapses months to years after original infection

Most important difference is *Plasmodium falciparum*'s ability to sequester in the microvasculature

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9. Sequestration

Sequestration

- As *P. falciparum* matures in the RBC it exports proteins to the RBC surface that form “knobs”.
- PfEMP1, a highly variant antigen found on the surface of these knobs allows the infected RBC to stick to various host receptors on the endothelium:
CD36, ICAM1, thrombospondin, CSA.
- Results:**
- Massive accumulation of infected red blood cells (IRBCs) in brain capillaries and other tissues.
- IRBCs avoid clearance through spleen

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10. Clinical manifestations

Clinical manifestations

- Uncomplicated malaria:**
- Prepatent period: 7-30 days, and if antimalarials are taken this can be longer
- Classical (but rarely observed):** a cold stage, followed by a hot stage (fever, headache vomiting, seizures in young children) and finally a sweating stage. Attacks occur every second day with *P. falciparum*, *P. vivax* and *P. ovale* (tertian), and every third day with *P. malariae* (quartan).
- More commonly patient presents with:**
Fever, chills, sweats, headache, nausea, vomiting, body aches and general malaise (sounds like the flu...) Combined with the long prepatent period this frequently leads to a misdiagnosis (in developed countries).

Additional findings (*P. falciparum*) may include: mild jaundice, enlarged liver and increased respiratory rate

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11. Clinical manifestations

Clinical manifestations

▶ **Severe malaria:**

Cerebral malaria: abnormal behavior, seizures, coma, other neurologic abnormalities

Severe anemia

Hemoglobinuria

Pulmonary edema and ARDS

Abnormalities in blood coagulation

Cardiovascular collapse and shock

Acute kidney failure

Metabolic acidosis

Hypoglycemia

- ▶ Severe malaria occurs most often in people with little or no immunity: young children, women in their first pregnancy, and travelers from non endemic areas.

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12. Pathogenesis:

Pathogenesis:

- ▶ Cerebral complications are probably not caused by blockage of capillaries, but by host immune responses to accumulation and adhesion of parasites in the capillaries.
- ▶ Anemia is more severe than can be accounted for by parasitemia and may involve immune mediated destruction of RBCs.
- ▶ Malaria parasites release GPI's (glycophosphatidylinositols) that induce release of pro-inflammatory cytokines: fever, edema and shock.

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13. Malaria – Virulence factors:

Malaria – Virulence factors:

- ▶ **Duffy blood group antigen:** Invasion into the RBC requires the presence of appropriate receptors. *P. vivax* requires the Duffy blood group antigen to gain entry into the RBC-since some Africans lack this receptor they cannot become infected with *P. vivax*
- ▶ **PfEMP1:** Knob associated erythrocyte surface antigen that mediates cytoadherence to endothelium, other IRBCs and uninfected RBCs . Protective immune responses are directed against this antigen-unfortunately it's variant (more on this latter).
- ▶

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14. Host genetics:

Host genetics:

- ▶ **Sickle cell trait:** Heterozygotes are protected from severe malaria-parasites grow poorly in RBC from people with this trait and the reasons are unclear.
- ▶ Other mediators of innate host resistance are glucose-6-dehydrogenase deficiency, β -thalassemia and ovalocytosis.

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15. Malaria - Immune Response

Malaria - Immune Response

- ☛ Immunity develops after long exposure and is not sterile: characterized by very low parasitemia
- ☛ Immunity is strain and species specific because protective IgG is directed against PfEMP1 which (as you now know) is variant.
- ☛ Adults in endemic areas have antibodies to all PfEMP1 variants
- ☛ If an immune adult moves out of the endemic area, the immune response declines and the person once again becomes susceptible.

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16. Malaria - Immune Response

Malaria - Immune Response

- ☛ Children develop antibodies as they become exposed to the different variants. Children will have anti-PfEMP1 antibodies to other strains but NOT to the strain they are currently infected with.
- ☛ Immune IgG mediates clearance of parasites in by two major mechanisms:
 - phagocytosis by macrophages
 - prevention of cytoadherence, forcing the mature IRBCs into the peripheral circulation where they are cleared by the spleen.

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17. Burden of Malaria in Pregnancy

Burden of Malaria in Pregnancy

- ☛ 45 million pregnancies in malaria-endemic areas
 - 23 million in high transmission areas of Africa
- ☛ Malaria contributes to negative health impact of both mothers and infants:

Mothers

- 3-15% of severe anemia
- up to 10,000 malaria anemia-related deaths per year

Infants

- 8-14% of all low birth weight
- 30% of preventable low birth weight
- 3-8% of infant mortality = 75,000-200,000 infant deaths/year

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18. Malaria in Pregnancy

Malaria in Pregnancy

As the placenta develops during pregnancy, it provides another organ for *P. falciparum* to sequester in.

In order to sequester in the capillaries of the placenta, the parasite expresses a new variant form of PfEMP1-one that is capable of adhering to Chondroitin sulfite A (CSA).

Since this variant has not been seen by the immune system before, there is no pre-existing immunity and complications of severe malaria can occur.

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19.

Diagnostic Options

Diagnostic Options

- ☞ Definitive diagnosis is based on the presence of parasites in Giemsa-stained thick and thin blood smears
- ☞ Thick smears more sensitive for detection of parasites
- ☞ Thin smears necessary for identification of *Plasmodium* species
- ☞ Histidine-rich protein 2 antigen assays
 - 92-96% sensitive –93-96% specific
- ☞ PCR

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20.

Blood Smear Features - Pf

Blood Smear Features - *Pf*

- ☞ *Plasmodium falciparum*
 - Normal size erythrocytes
 - Small ring forms common-
 - do not see mature stages!! (Why?)
 - Multiply infected cells
 - High grade parasitemia
 - Rare banana shaped gametocytes

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21.

Blood Smear Features - Pv

Blood Smear Features - *Pv*

☞ *Plasmodium vivax*

- Enlarged erythrocytes
- Schüffner's stippling
- Ameboid trophozoites

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22.

Treatment and prevention

Treatment and prevention

Anti-malarials and insecticides:

Resistance is a HUGE problem

No vaccine

One fairly successful
approach: bednets

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23. Efficacy of Bednets for Reduction of Malaria Mortality

Efficacy of Bednets for Reduction of Malaria Mortality

- ☛ Gambia: 63% decrease in all-cause mortality in children aged 1-4 y
 - Alonso P et al. Lancet 1991
- ☛ Ghana: 17% decrease all-cause mortality in children aged 6 mo–4 y
 - Binka FN et al. Trop Med Int Health 1996
- ☛ Kenya: 30% decrease all-cause mortality in children aged 1-5 y
 - Nevill CG et al. Trop Med Int Health 1996

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24. Problems with Bednets

Problems with Bednets

- ☛ Acceptance
- ☛ Require periodic reimpregnation
- ☛ Cost
- ☛ Use may influence the rate and timing of the acquisition of immunity to malaria
 - Will use lead to a shift towards more cerebral malaria in older age groups?
 - Will incomplete use lead to greater mortality in older age groups?

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25.

Mosquito Control Measures

Mosquito Control Measures

- ☛ Destruction of mosquito larvae
 - Larvicides
 - Increasing salinity of standing water
 - Introduction of predators
- ☛ Prevention or reduction of breeding
 - Elimination of standing water by drainage, filling, etc.
- ☛ Destruction of adult mosquitoes
 - Insecticides
 - Permethrin-treated bednets

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26.

Malaria: *Babesia microti*

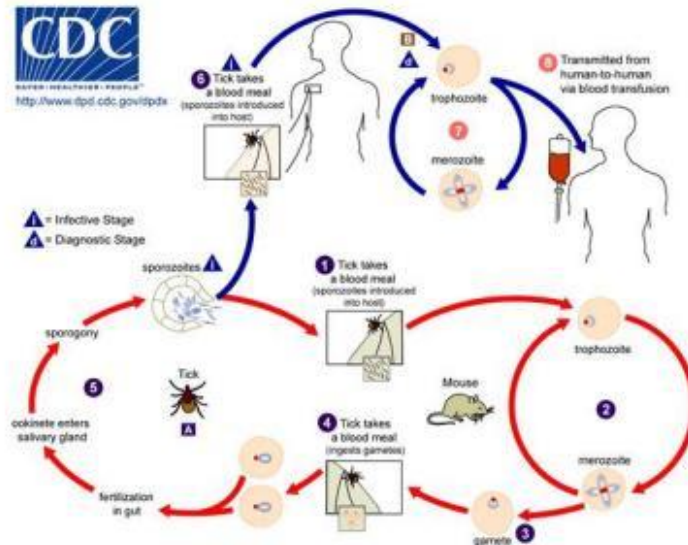
Babesia microti:

Tick transmitted, intraerythrocytic
apicomplexan

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27.

Malaria: Slide 27



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28.

Babesia microti

Babesia microti

- **Important points**
- *Ixodes scapularis*: tick vector (and definitive host)-also transmit Lyme disease
- Animal reservoir: White footed mouse
- There are no exo-erythrocytic stages in the mammalian host
- Sexual stages have not been identified
- **Diagnosis:** Giemsa stained blood smear
- **Treatment:** clindamycin and quinine, or atovaquone and azithromycin (point: different from malaria)

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