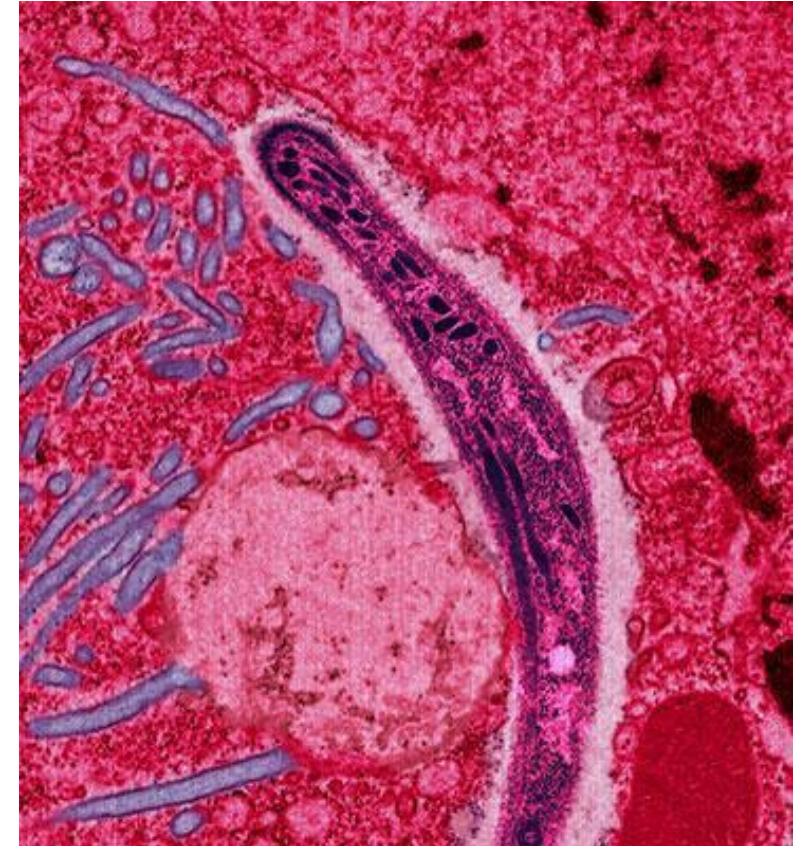


Week 2: Malaria and Natural Products

Malaria Basics

- Caused by parasites called protozoans
 - *Plasmodium* (5 types)
 - *P. falciparum* is most deadly, *P. vivax* outside sub-Saharan Africa
- Transmitted by infected female mosquitos
 - *Anopheles* (30/400 species)
- Transmission is frequently worse during or after rainy season



Plasmodium in mosquito saliva

Symptoms

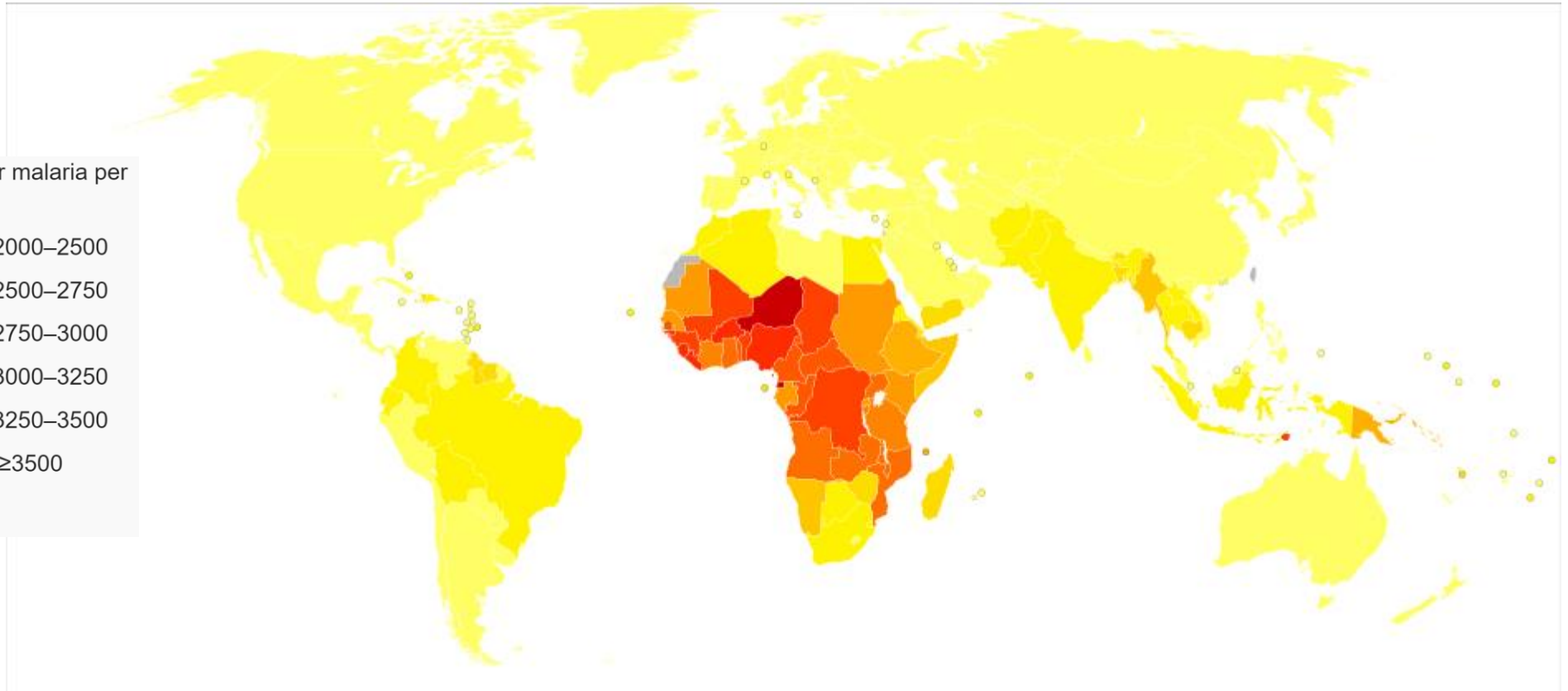
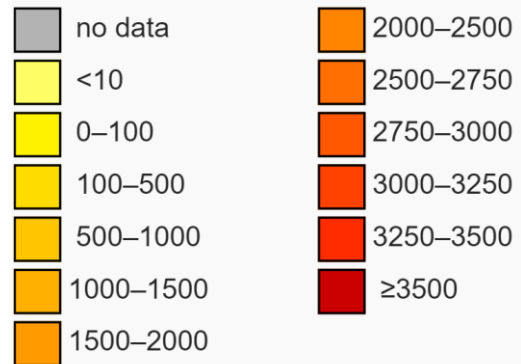
- Initial infection occurs in the liver (8-30 days)
- Spreads to red blood cells, reproduce, burst, repeat
- Symptoms usually begin 10-15 days after infection
- Fever, fatigue, vomiting, headaches, seizures, coma, death



Child with malaria, Ethiopia

Range

Disability-adjusted life year for malaria per 100,000 inhabitants in 2004



Disease Burden

- 214 Million cases in 2015
- 428,000 deaths in 2015
- 65% of cases in people younger than 15
- Good progress since 2000:
 - Incidence down 37%
 - Mortality rate down 60%



Prevention: Vector Control

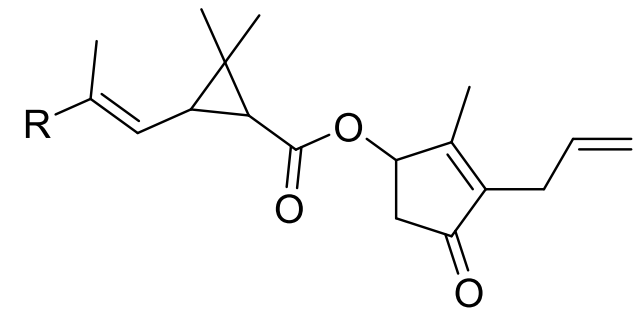
- Insecticide-treated nets are most effective
 - Mosquitos primarily feed at night
 - Must be properly maintained and used
- Indoor spraying of insecticides
 - Works best when at least 80% of houses are targeted
 - Effective for 3-6 months



Bed enclosed by long-lasting insecticidal net (LLIN)

Insecticide Resistance

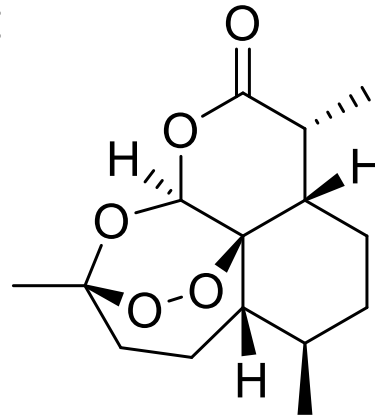
- Resistance is developed by mosquitos, not plasmodium
- Pyrethroids are only recommended class
- Insecticide-resistance is becoming prevalent
- Some nets are now treated with two drugs
- Monitoring and new drug development are critical



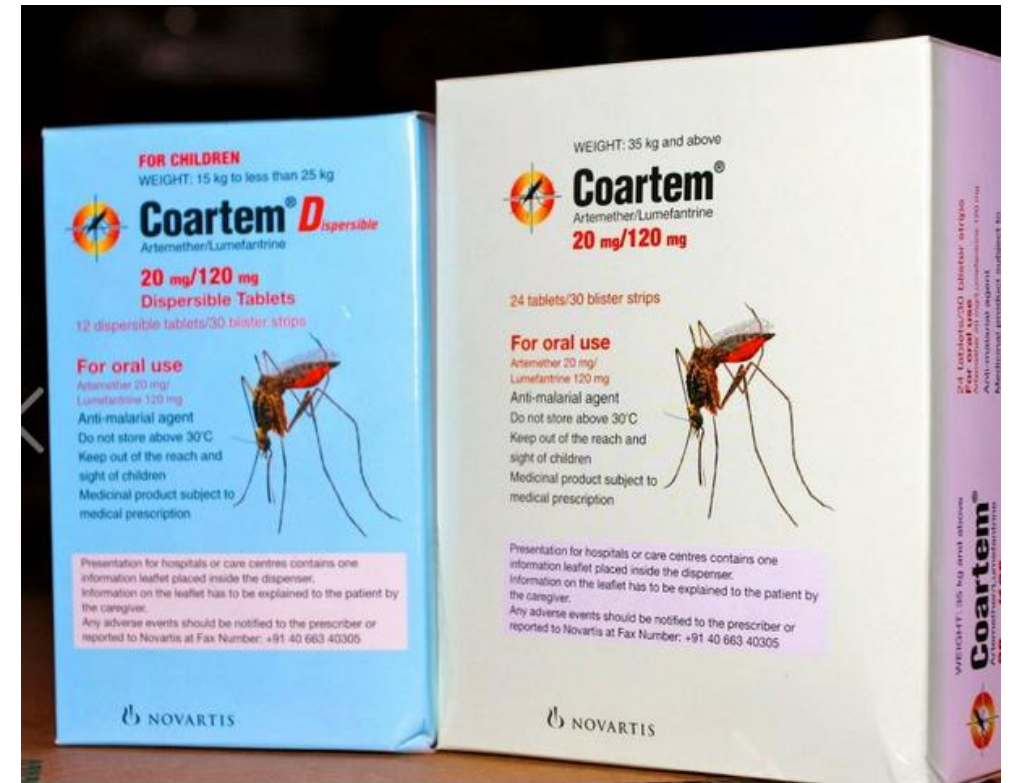
Typical pyrethoid structure

Malaria Treatment

- Preventative drugs available
 - Sulfadoxine-pyrimethamine
- Best treatment is artemisinin-combination therapy
 - Must confirm diagnosis first
 - Must not be used alone
 - **Resistance has developed**
 - More costly than others

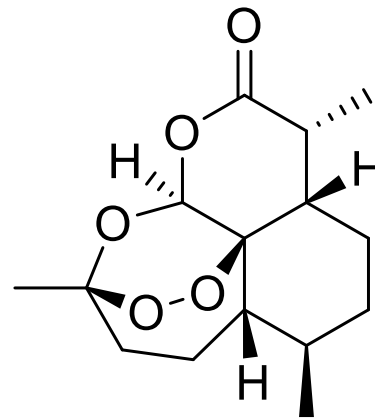


artemisinin



Artemisinin: A Natural Product

- Drug can be isolated from sweet wormwood
- Has been used for malaria treatment for over 2000 years
- Discovered in 1967 by Tu Youyou
 - Shared Nobel prize in 2015
- Likely acts via endoperoxide

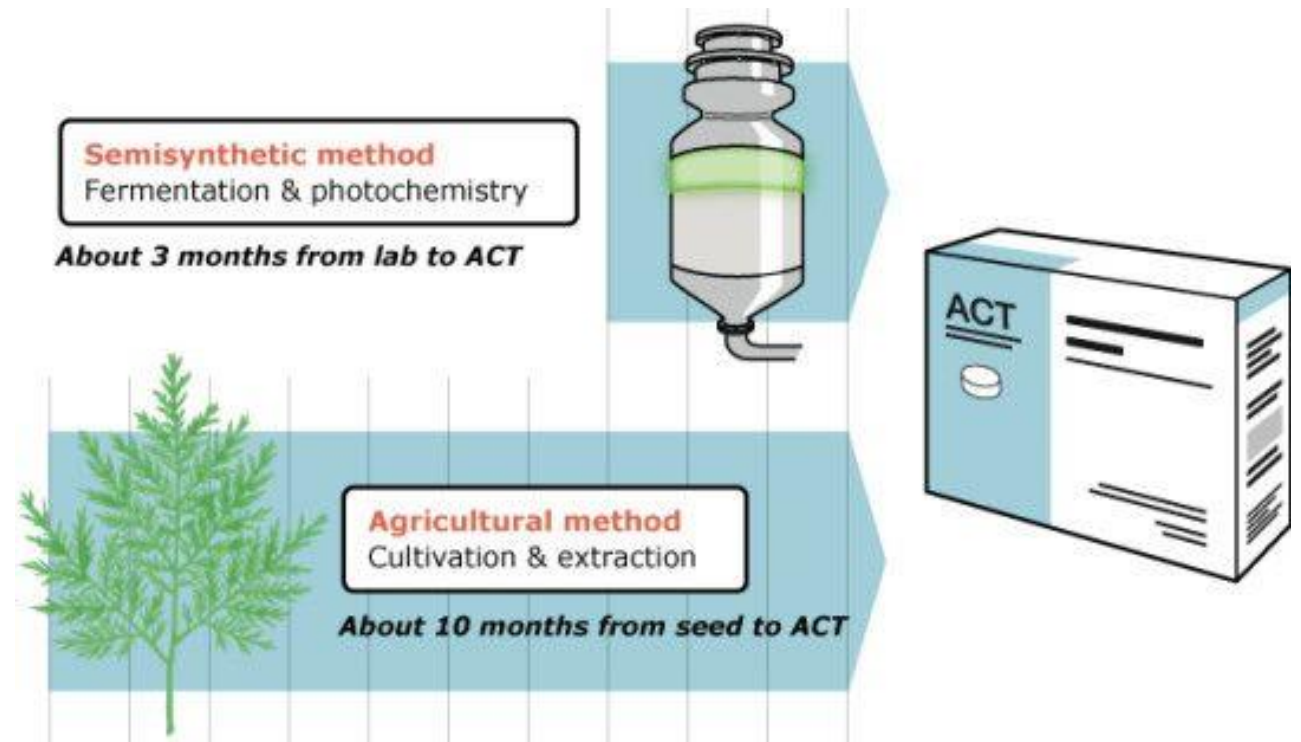


artemisinin

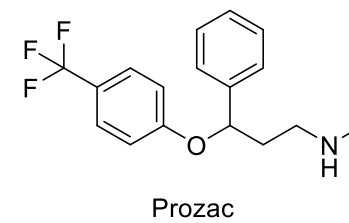
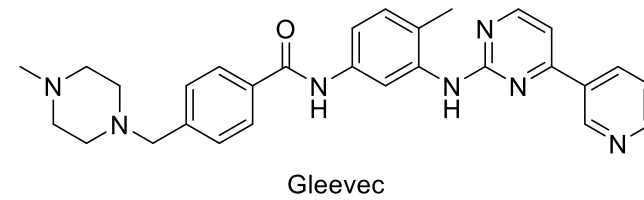
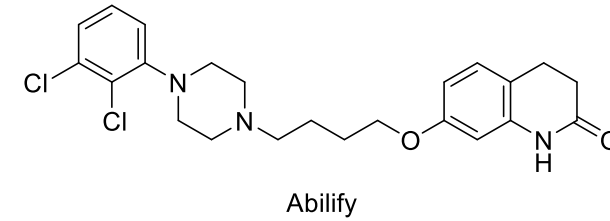
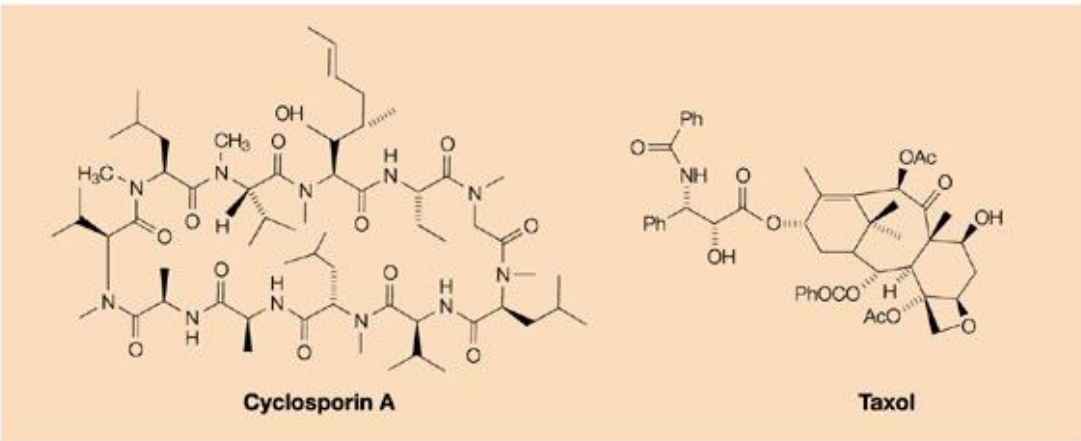
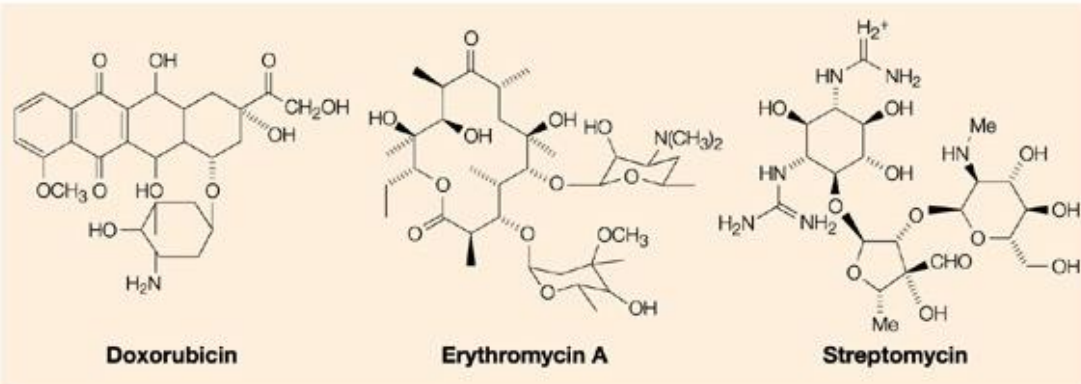


Artemisinin Three Ways

- Biosynthesis
- Chemical Synthesis
 - 13 steps, ~5% yield
- Semi-synthesis
 - Uses genetically engineered yeast
 - 3 steps, ~30% yield



Natural Products vs. Synthetics



Natural Products Overview

- Sources:
 - Bacteria, Fungi, Plants, Animals, Marine Life
- Testing crude extracts
- Isolating the natural product
- Characterizing natural product
- Further development: isolation vs. synthesis vs. semisynthesis

