Week 2: Malaria and Natural Products
The Deadliest Disease in Human History

• Responsible for ½ of human deaths since the stone age
• Mosquitos are by far the deadliest animal, largely because of malaria
• (Not a neglected tropical disease)
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 mosquitoes
  • *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
Range

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

- no data
- <10
- 0–100
- 100–500
- 500–1000
- 1000–1500
- 1500–2000
- 2000–2500
- 2500–2750
- 2750–3000
- 3000–3250
- 3250–3500
- ≥3500
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
• Pyrethoids are only recommended class
• Insecticide-resistance is becoming prevalent
• Some nets are now treated with two drugs
• Monitoring and new drug development are critical
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: 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 Three Ways

• Biosynthesis
  • 13 steps, ~5% yield

• Chemical Synthesis
  • 13 steps, ~5% yield

• Semi-synthesis
  • Uses genetically engineered yeast
  • 3 steps, ~30% yield
Natural Products vs. Synthetics

Doxorubicin
Erythromycin A
Streptomycin

Cyclosporin A
Taxol

Abilify
Gleevec
Prozac

Nature Reviews | Drug Discovery
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