Antimalarial Drugs

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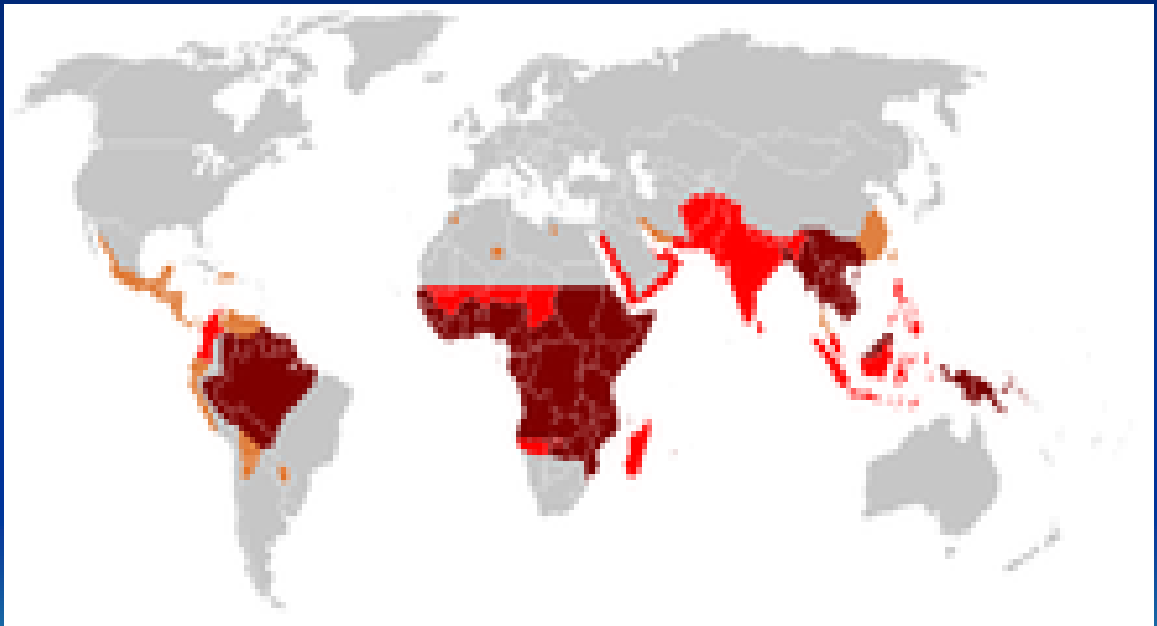
Malaria

- In 2017, there were an estimated 219 million cases of malaria(296 million in 2015) which resulted in an estimated 453,000 deaths.



Antimalarial Treatment

- **SuppressiveTreatment (المعالجة القمعية)= Clinical Cure:** Chloroquin, Quinine, Quinidine , Doxycyline, Clindamycin, Mefloquine, and Halofantrine.

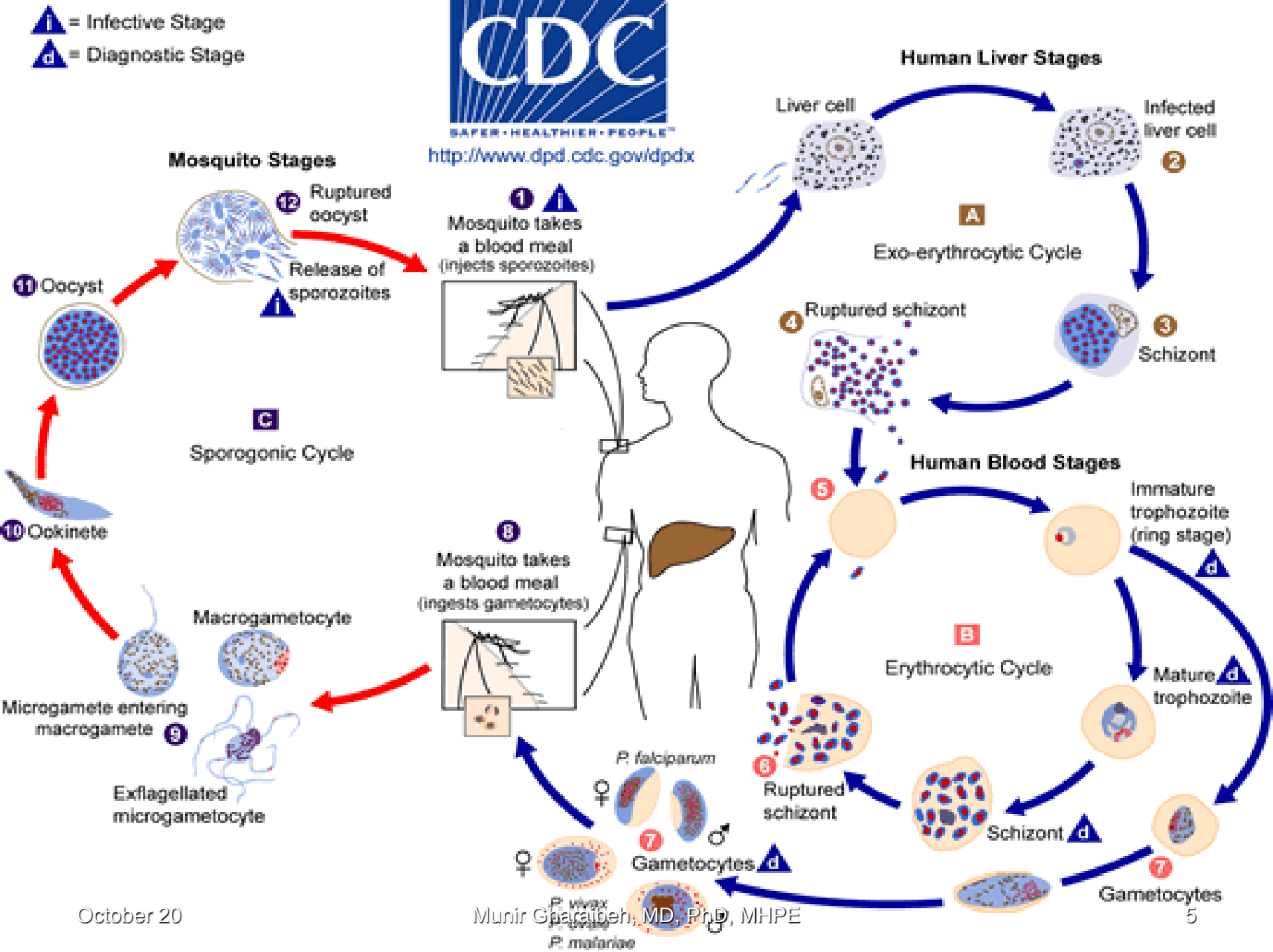
- **Radical Cure(المعالجة الجذرية)**: Chloroquin followed by Primaquine, required for *P vivax and P ovale*.

- **Prophylaxis**: Chloroquin, Mefloquin, ”Malarone”, and Doxycycline.

Malarial Parasites

- ***Plasmodium falciparum***

  (only erythrocytic, **serious, resistance*****).***
- ***Plasmodium vivax.***
- ***Plasmodium malariae.***
- ***Plasmodium ovale.***


= Infective Stage
= Diagnostic Stage
CDC
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http://www.dpd.cdc.gov/dpdx
Human Liver Stages
Liver cell
Infected liver cell
A
Exo-erythrocytic Cycle
Ruptured schizont
Schizont
Human Blood Stages
Immature trophozoite (ring stage)
Mature trophozoite
B
Erythrocytic Cycle
Ruptured schizont
Schizont
Gametocytes
Gametocytes
P. falciparum
P. vivax
P. malariae
Mosquito Stages
Ruptured oocyst
Release of sporozoites
Mosquito takes a blood meal (injects sporozoites)
Oocyst
C
Sporogonic Cycle
Ookinete
Mosquito takes a blood meal (ingests gametocytes)
Macrogametocyte
Microgamete entering macrogamete
Exflagellated microgametocyte

Chloroquine

Synthetic 4-Aminoquinolone

Specific uptake mechanism is present in the parasite, the drug accumulates in the parasite to inhibit polymerization of heme into hemozoin and thus parasite is poisoned by heme.

Well absorbed, distributed, bound to tissues.

Chloroquine

Schizonticide for all four types of malaria.

Drug of choice in the treatment of nonfalciparum and sensitive falciparum malaria.

Does not eliminate dormant liver forms of *P. vivax* and *P.* ovale, so, Primaquine must be added for their radical cure.

Chloroquine

Resistance:

Very common with *P. falciparum* and increasing with *P.vivax.*

Due to mutation in P170 glycoprotein (PfCRT) works as a drug-transporting pump mechanism .

Chloroquine

- **Very practical, convenient(oral), rapid action, low cost, and safe.**
- **Started immediately after diagnosis.**
- **Other doses are given after 6 hours, 24 hours and last dose after 48 hours.**
- **However, does not eliminate dormant liver forms of *P.vivax and P.ovale.***

Chloroquine

Also effective in:

- **Rheumatoid arthritis.**
- **LE.**
- **Amebic liver abscess.**
- **Photoallergic reactions.**
- ***Clonorchis sinensis.***

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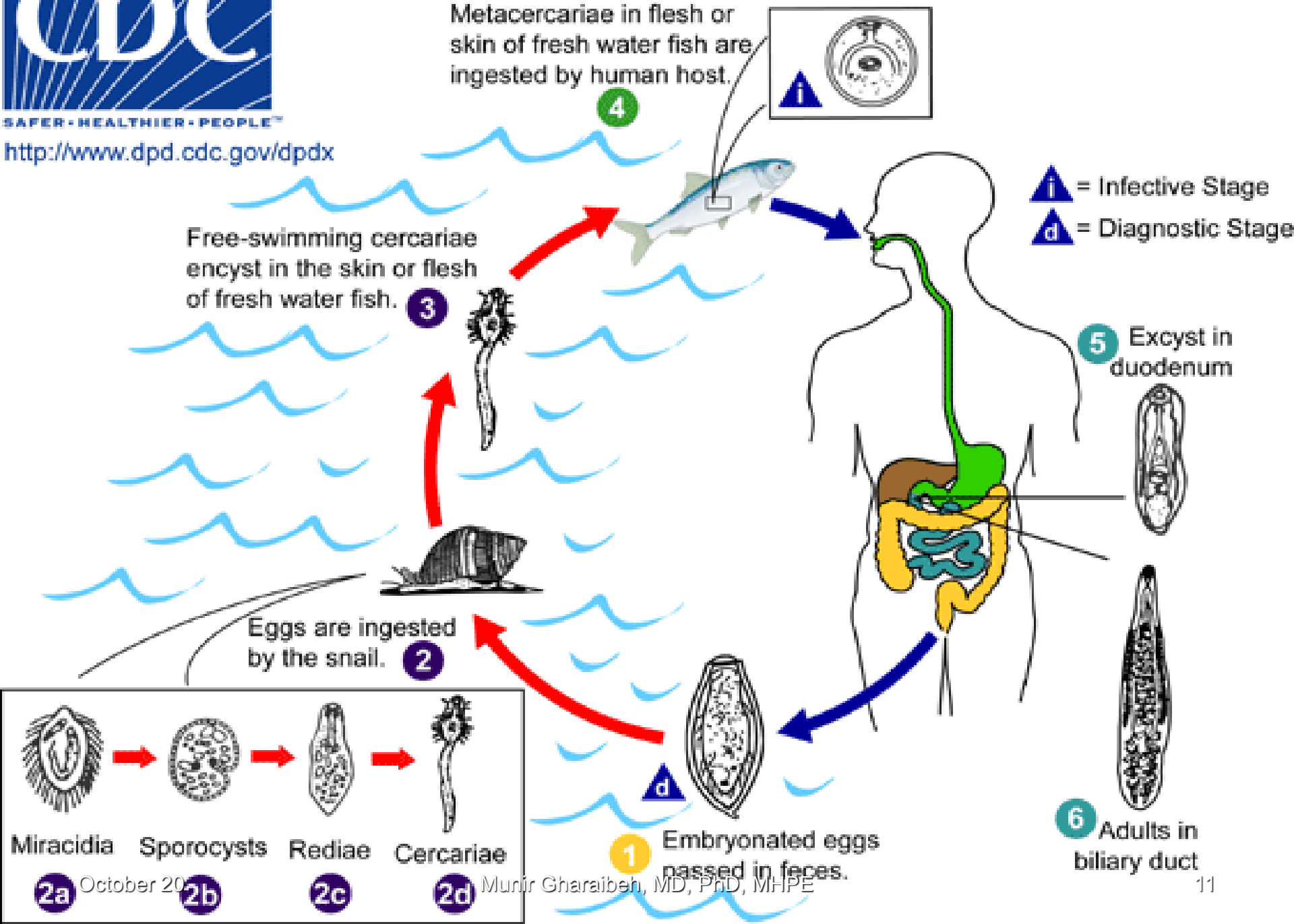


Chloroquine

Side Effects:

- Headache, dizziness,
- Itching and rash,
- Nausea, vomiting, anorexia
- Unmasking of LE, psoriasis and porphyria.
- Corneal deposits, blindness, blurring of vision,

Quinine(1820) and Quinidine

Cinchona tree from

South America.

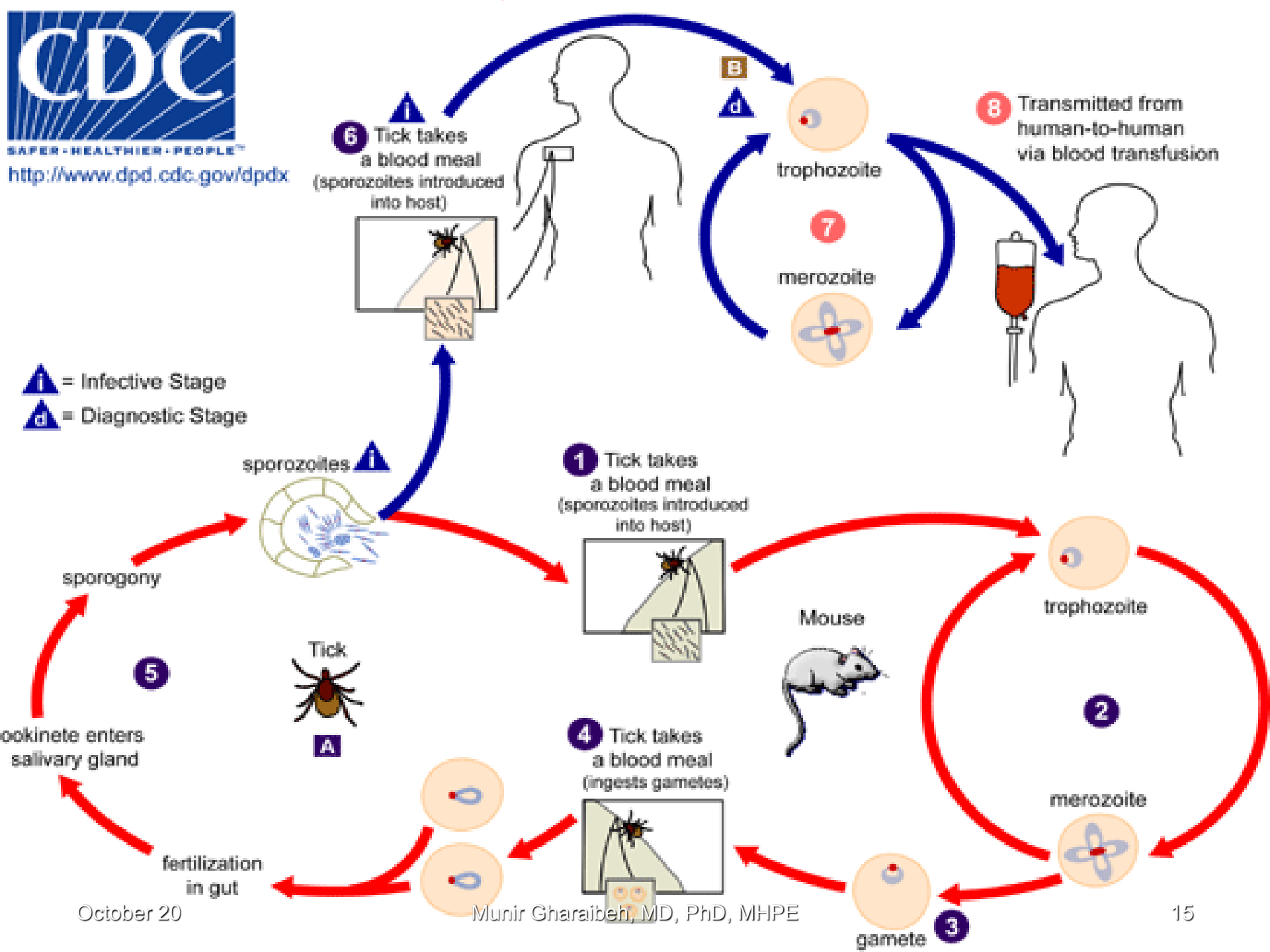
General protoplasmic poison: will affect the feeding mechanism of the parasite.

Resistance is uncommon.

Effective rapid schizonticide therapy for severe falciparum, chloroquine-resistant malaria, usually in combination with another drug (e.g. Doxycycline or Clindamycin) to shorten duration of use.

Quinine and Quinidine

- Also effective for *Babesia microti* infection.
- Also, for nocturnal leg muscle cramps (Arthritis, DM, thrombophlebitis, arteriosclerosis, varicose veins)


CDC
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i = Infective Stage
d = Diagnostic Stage
6 Tick takes a blood meal (sporozoites introduced into host)
B
d
trophozoite
7
merozoite
8 Transmitted from human-to-human via blood transfusion
sporozoites
i
1 Tick takes a blood meal (sporozoites introduced into host)
trophozoite
Mouse
2
merozoite
sporogony
5
Tick
A
ookinete enters salivary gland
4 Tick takes a blood meal (ingests gametes)
fertilization in gut
gamete
3

Quinine and Quinidine

Adverse Effects:

Cinchonism: **Tinnitus, headache, nausea, dizziness, flushing, visual disturbances. Later, auditory abnormalities, vomiting, diarrhea, and abdominal pain.**

Blood dyscrasias.

Hypersensitivity, hypoglycemia, uterine contractions.

Hypotension, QT prolongation.

Blackwater fever (hemolysis, hemoglobinemia, hemoglobinurea, and renal failure)

Mefloquine

- Blood schizonticide, not for liver forms.
  Used for resistant *P. falciparum* (single oral dose).

  Also for suppressive and prophylactic treatment (weekly doses).
- Nausea, vomiting, diarrhea, pain.
- Vertigo, dizziness, headache, rashes and visual alterations.
- Psychosis, hallucinations, confusion, anxiety, depression.

Primaquin

- 8-aminoquinolone
  Unknown mechanism.
  Drug of choice; the only available one, for eradication of exoerythrocytic forms of malaria after treatment with chloroquin.

  Hemolysis in G6PD deficient patients.
  Also, nausea, distress, headache, pruritis, leukopenia and agranulocytosis.

Atovaquone and Proguanil

- Usually in fixed combination = “Malarone”.
- Recommended drug for prophylaxis.

- Atovaquone also approved for *P. jiroveci* pneumonia, although has lower efficacy than Trimethoprim-sulfamethaxazole combination.

- Can cause fever, rash, nausea, vomiting, diarrhea, headache, and insomnia.

Pyrimethamine

Inhibits DHF Reductase

Slow and long acting drug.

Effective on erythrocytic forms of all species.

Not for severe malaria.

Preferential binding to parasitic enzyme.

Usually combined with Sulfadoxine" Fansidar" or Sulfones which inhibit Dihydropteroate synthase.

No longer recommended for prophylaxis.

Also, for *Toxoplasmosis*(in higher doses), and *P. jeroveci.*

Pyrimethamine

Adverse Effects:

Anorexia, Vomiting, Leucopenia, Thrombocytopenia, glossitis

CNS: Stimulation, Convulsions

Allergic reactions including Stevens-Johnson Syndrome

Antibiotics

- Tetracycline.
- Doxycycline.
- Clindamycin.
- Azithromycin.
- Fluoroquinolones.

Active against erythrocytic forms of all species.

Usually for chloroquine-resistant strains.

Also effective against other protozoal diseases.

Halofantrine and Lumefantrine

- Rapidly effective against erythrocytic forms of all species.
- Usually for chloroquine-resistant strains.
- Well tolerated, except for cardiac toxicity (QT prolongation)

Artemisnin= Qinghaosu

- Artesunate.
- Artemether.
- Derivatives of Artemisia(الشيح) used by Chinese since 2000 years.
- Rapidly acting schizonticides against all species.
- No documented resistance.
- Work by free radical formation or ATP inhibition.
- Only drugs reliably effective against quinine-resistant and multi-drug resistant strains.
- High cost, unavailable.
- N.V.D, and neurotoxicity in animals.

Drugs for Leishmania

Caused by three *Leishmania species:*

***L.tropica* causes: Cutaneous leishmaniasis or oriental sore.**

***L. brazeliensis* causes: Mucocutaneous leishmaniasis.**

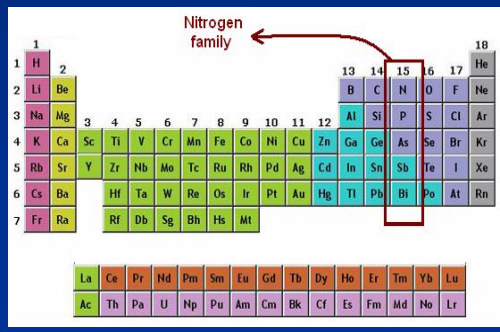
***L. Donovani* causes: Visceral leishmaniasis**

Sodium Stibogluconate

Pentavalent Antimony (الأثمد) :

Binds to SH groups on proteins.

Contains 30% to 34% pentavalent antimonyby weight as well as *m*-chlorocresol added as a preservative.



Also, inhibits phosphofructokinase

Local, IM or slow IV, irritant.

Given for 20-28 days.

Drug of choice for all forms of leishmaniasis.

Resistance is increasing, especially in India.

Cough, V, D, myalgia, arthralgia, ECG changes, Rash, Pruritus.

Amphotericin B

- Antifungal agent, difficult to use, and toxic.
- Alternative therapy for visceral leishmaniasis, especially in areas with high resistance.

Miltefosine

- For visceral leishmaniasis.
- Given orally, for 28 days.
- Causes V & D, hepatotoxicity, nephrotoxicity, and teratogenicity.

Pentamidine

- Inhibits DNA replication.
- Also, DHF reductase inhibitor

- Given by IM or IV injection and Inhalation
- Binds avidly to tissues, but not to the CNS.

Pentamidine

Leishmaniasis:

Alternative to Na stibogluconate

Pneumocystis jiroveci:

Treatment and prophylaxis of patients who cannot tolerate or fail other drugs.

Trypanosomiasis:

For early hemolymphatic stage.

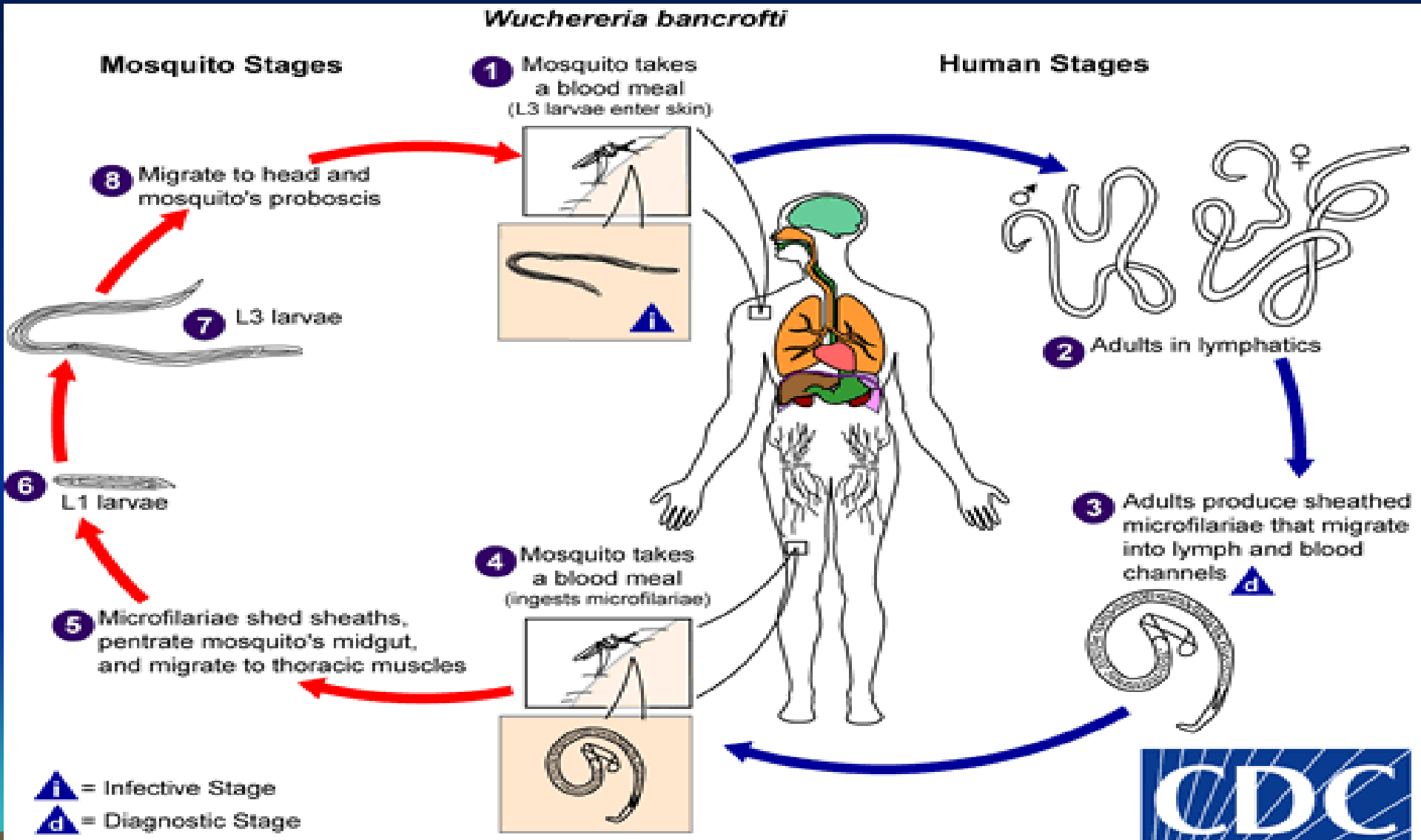
Pentamidine

- **<u>Adverse Effects:</u>**
- **Rapid Infusion: Hypotension, tachycardia, dizziness.**
- **Pain at the injection site.**
- **Others: Pancreatic, Renal, and Hepatic toxicity.**

Diethylcarbamazine

- The drug of choice in the treatment of filariasis, loiasis, and tropical eosinophilia.
- May also be used for mass treatment and chemoprophylaxis.

Filariasis


Wuchereria bancrofti
Mosquito Stages
Human Stages
1 Mosquito takes a blood meal
(L3 larvae enter skin)
2 Adults in lymphatics
3 Adults produce sheathed microfilariae that migrate into lymph and blood channels
4 Mosquito takes a blood meal
(ingests microfilariae)
5 Microfilariae shed sheaths, pentrate mosquito's midgut, and migrate to thoracic muscles
6 L1 larvae
7 L3 larvae
8 Migrate to head and mosquito's proboscis
i = Infective Stage
d = Diagnostic Stage

Lymphatic Filariasis

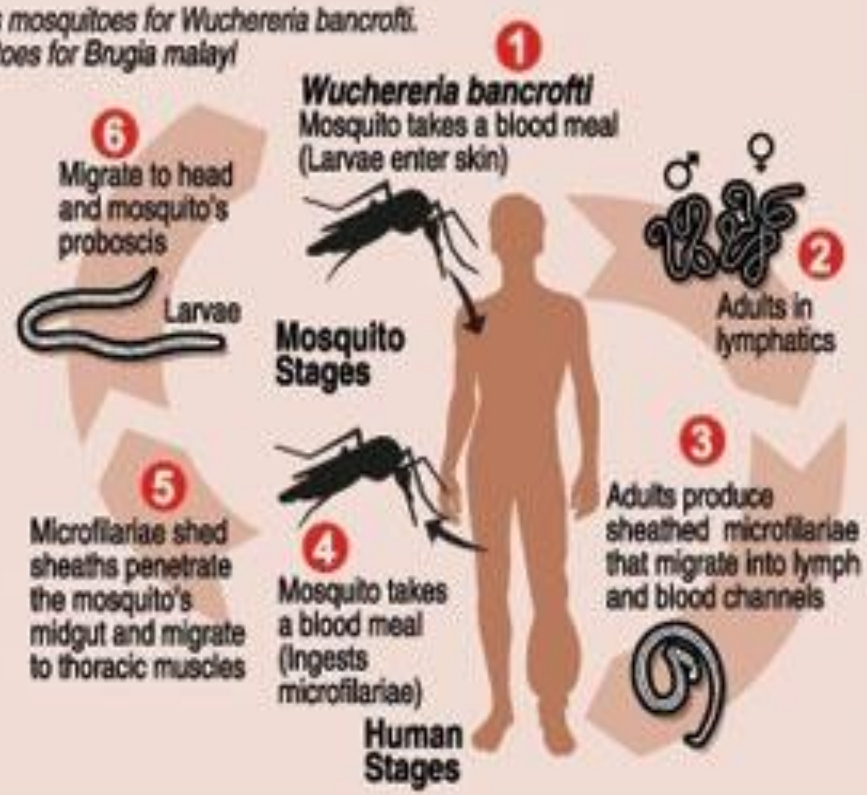
Parasitic disease caused by an infection with round worms. Two types of filarial parasites have been reported in Sri Lanka - *Wuchereria bancrofti (majority) and Brugia malayi*

Transmission:
Culex quinquefasciatus mosquitoes for Wuchereria bancrofti.
Mansonia spp. mosquitoes for Brugia malayi

Breeding sites:
- *Improperly sealed septic tanks*
- *Waste water pits*
- *Blocked drains*
- *Water bodies with aquatic plants for Mansonia species*

Incubation period:
8-16 months

Symptoms:
Asymptomatic and chronic conditions. The majority of infections are asymptomatic



Develop into adult worms in the lymphatic vessels, causing severe damage and swelling. Elephantiasis – painful, disfiguring swelling of the legs and genital organs

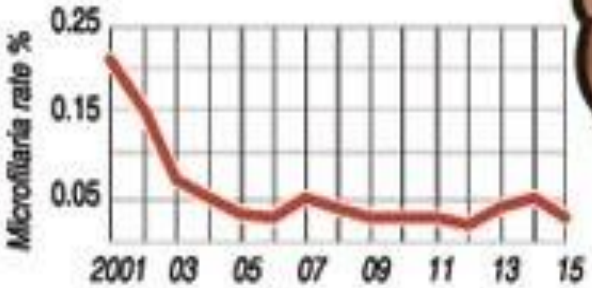
Microfilariae can be detected in the peripheral smear.

Sri Lanka has successfully brought down the microfilaria rate to less than 1%

Distribution and status of preventive chemotherapy

- *Endemic countries and territories implementing preventive chemotherapy*
- *Endemic countries and territories where the target was achieved and implementation stopped*
- *Endemic countries and territories not implementing preventive chemotherapy*

Microfilaria Rate In Sri Lanka (2001-2015)



ST Infographics: Nalin Balasuriya

Sources: WHO, Anti Filariasis Campaign, Centers for Disease Control and Prevention

PEPSI

Diethylcarbamazine

- Immobilizes microfilariae and alters their surface structure, displacing them from tissues and making them more susceptible to destruction by host defense mechanisms.
- The mode of action against adult worms is unknown.
- Plasma half-life is 2–3 hours in the presence of acidic urine but about 10 hours if the urine is alkaline.

Diethylcarbamazine

- Reactions to dying microfilariae are usually mild in *W. bancrofti* , more intense in *B. malayi* , and occasionally severe in *L. loa* infections(fever, malaise, papular rash, headache, gastrointestinal symptoms, cough, chest pain, and muscle or joint pain, leukocytosis, eosinophilia, proteinuria) in patients with heavy loads of microfilariae. Retinal hemorrhages and, rarely, encephalopathy have been described.
- Antihistamines and corticosteroids might be needed to reduce allergic reactions.

Ivermectine

- Ivermectin appears to paralyze nematodes and arthropods by intensifying γ-aminobutyric acid (GABA)

- Filariasis
- Onchocerciasis
- Strongyloidiasis
- Also for scabies, lice, and cutaneous larva migrans

Ivermectin

- Occasionally induces severe reactions and appears to be more dangerous in this regard than diethylcarbamazine

Doxycycline

- Recently shown to have significant macrofilaricidal activity against *W. bancrofti* , suggesting better activity than any other available drug against adult worms.
- Onchocerciasis.
- Acts indirectly, by killing Wolbachia.
- For both treatment of active disease and in mass chemotherapy campaigns.