Department of Infectious Diseases
University Hospital Brno

Malaria, Schistosomiasis, Tetanus

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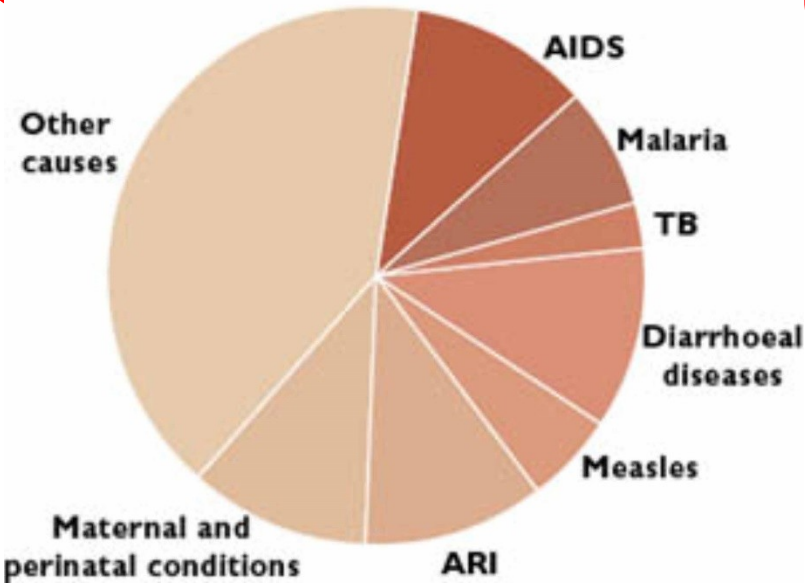
As you know, in the developing world treatable infectious diseases remain big killers...

HIV/AIDS, Tuberculosis and Malaria: The basic facts, 2002 (World Health Organization)			
Disease	Deaths per year	New cases per year	Percentage in developing countries
HIV/AIDS	3 million	5.3 million	92%
Tuberculosis	1.9 million	8.8 million	84%
Malaria	1 million	300 million	99.9%



Leading causes of death in Sub-Saharan Africa, South Asia, and Southeast Asia for persons age 0-44 (World Health Organization, 2015)

Now it's time to look at number 3:
Malaria!

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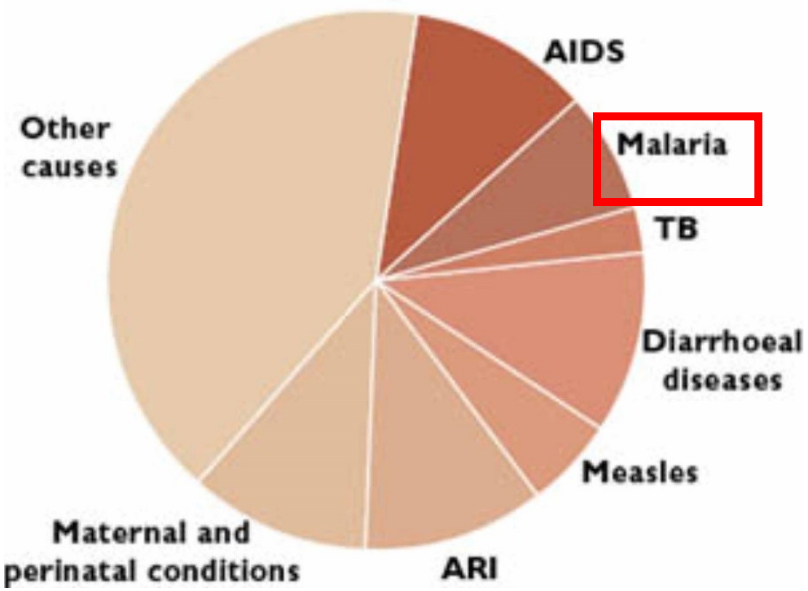

Leading causes of death in Sub-Saharan Africa, South Asia, and Southeast Asia for persons age 0-44 (World Health Organization, 2015)

That's right:
300 million new cases per year
making it the most prevalent serious infectious disease!

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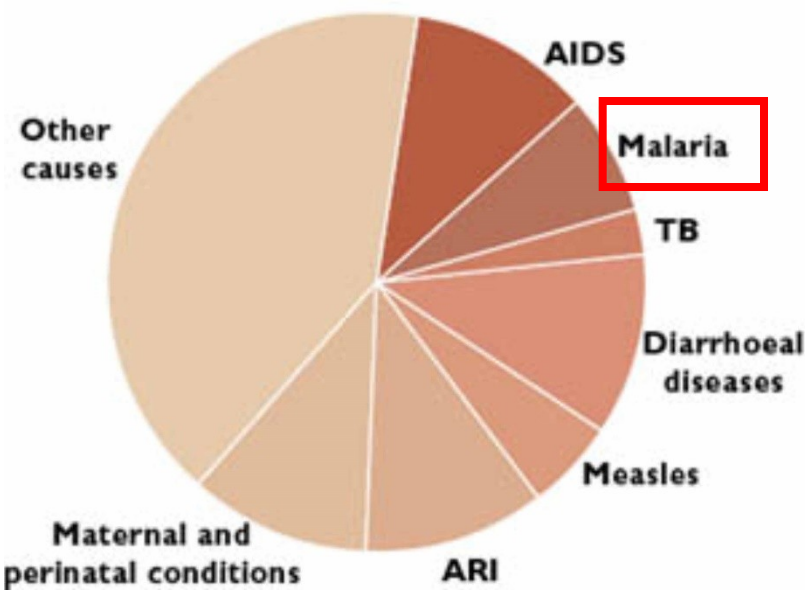


Leading causes of death in Sub-Saharan Africa, South Asia, and Southeast Asia for persons age 0-44 (World Health Organization, 2015)

Malaria - History

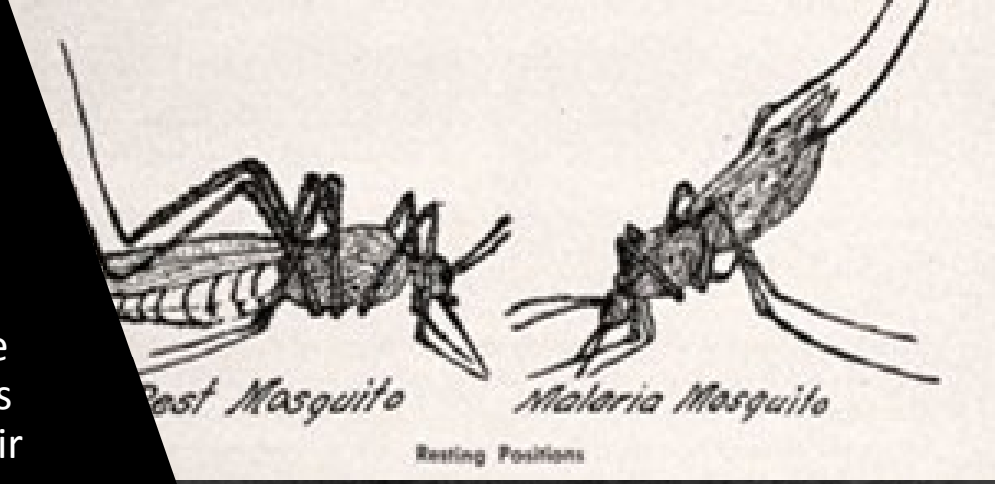
Febrile illness known already in ancient Greece and Sumeria. The name **mall'aria** - "bad air," as the cause of the disease was considered bad air **around the standing waters.**

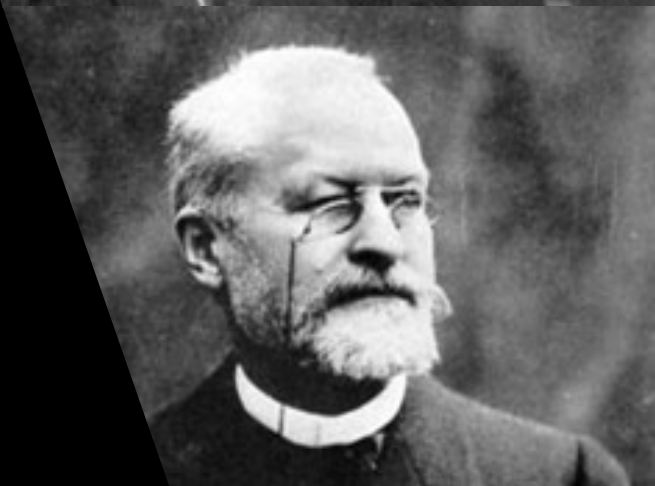
Sir Patrick Manson - the second half of the 18th century, was obsessed with the idea that malaria was carrying mosquitoes, he was not taken seriously - **"Mosquito (crazy) Manson".**

To confirm his theory, he brought mosquitoes from an Italian hospital to London, where he had the mosquitoes suck on his eldest son. The young Manson really got sick **(survived but treated for 1 year).**

French physician **Charles Laveran** in 1880 observed in the blood of a sick soldier a protozoan ***Plasmodium***.

Later, the presence of ***Plasmodium*** was demonstrated in the bowels of the *Anopheles* mosquito. **In 1907 he received the Nobel Prize.**





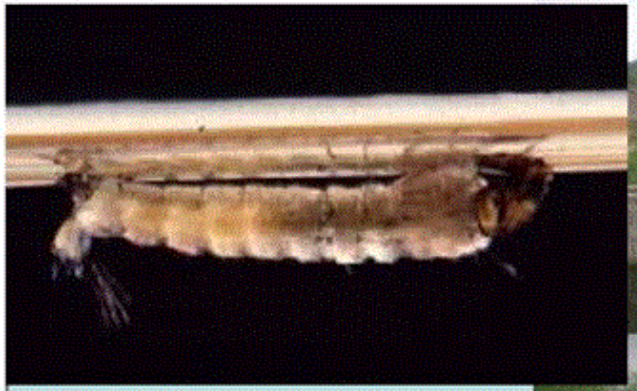
Etiology of Malaria

- Malaria is caused by a parasite of the genus *Plasmodium* – a single celled organism that cannot survive outside of their host
- The vectors of the infection are female mosquitoes of the genus *Anopheles*

Agent	Form	Incubation period	Period of burst	Severity	Possibility of relapses
P. vivax	Tertian	8-28 d.	48 h.	Benign	Yes
P. ovale	Tertian	8-28 d.	48 h.	Benign	Yes
P. malariae	Quartan	18-42 d.	72 h.	Benign	No
P. falciparum	**Tropica**	**8-28 d.**	**24-48 h.**	**Malignant**	**No**
P. knowlesi	**Quotidian**	**12 d.**	**24 h.**	**Malignant (sometimes)**	**No**

Mosquitoes of the genus *Anopheles* - Transmitters of Malaria

Anopheles gambiae

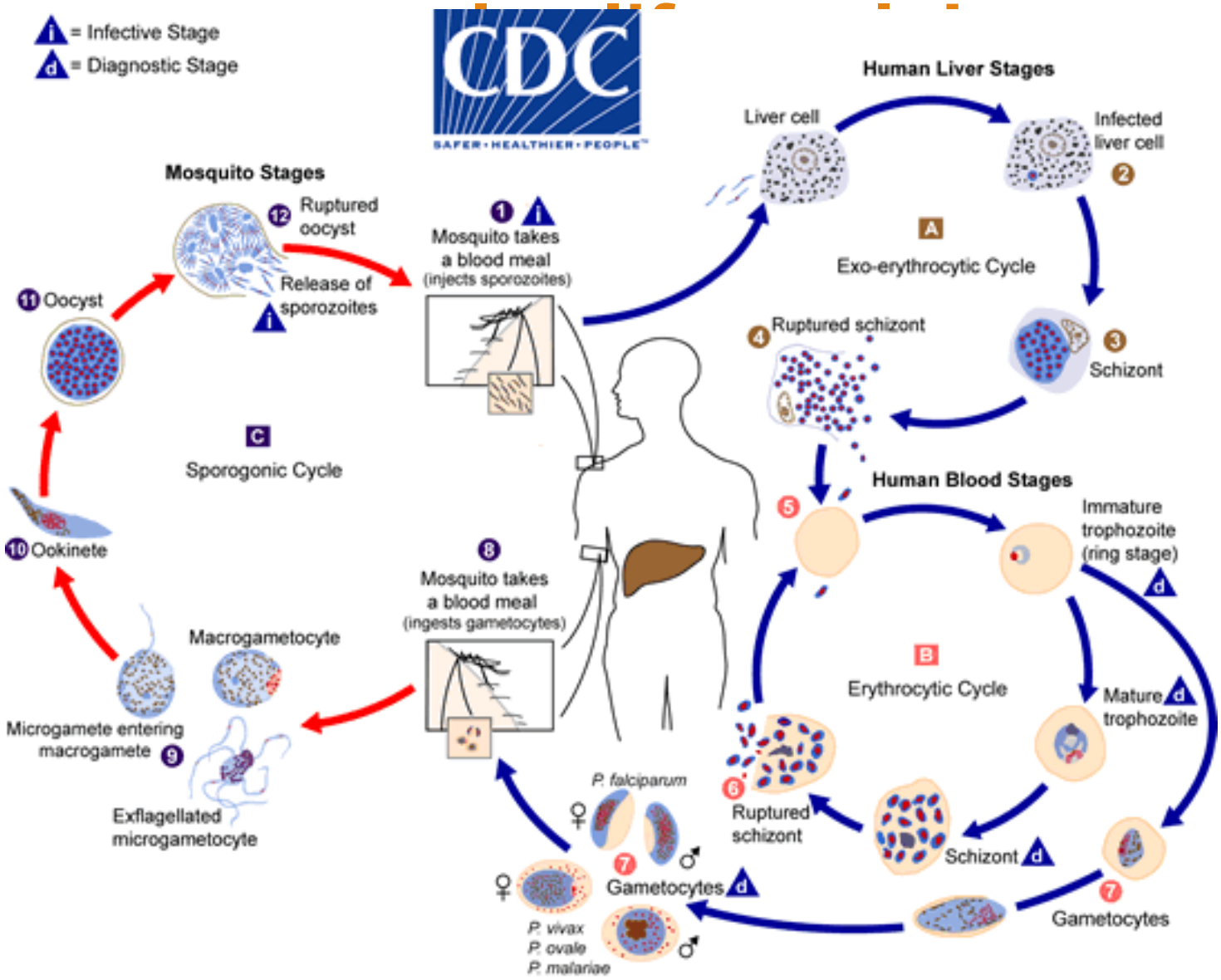


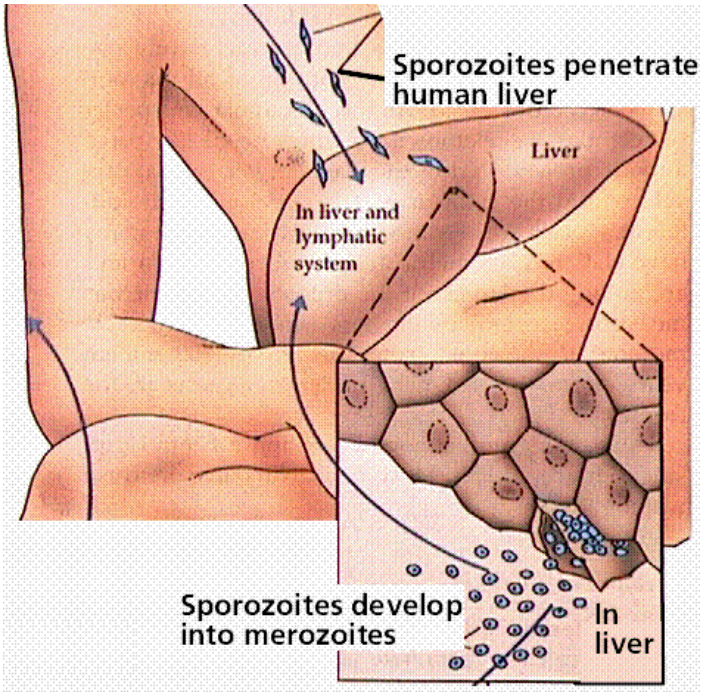
Anopheles sp. - larva

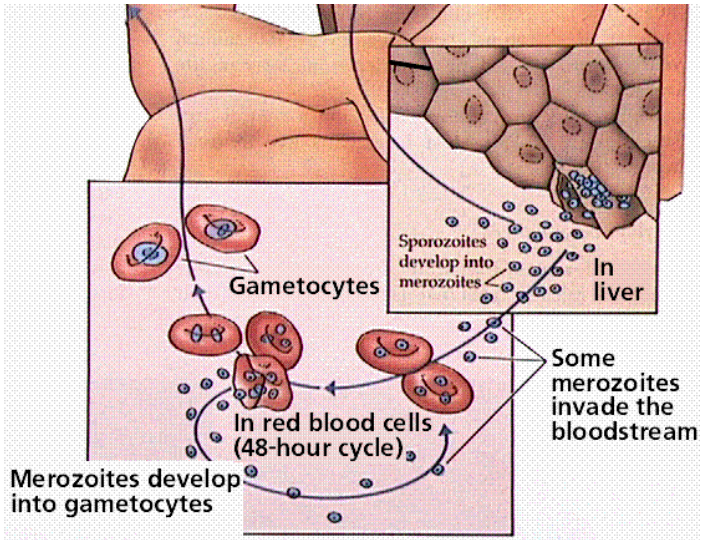
„Breeding grounds“ for mosquitoes:

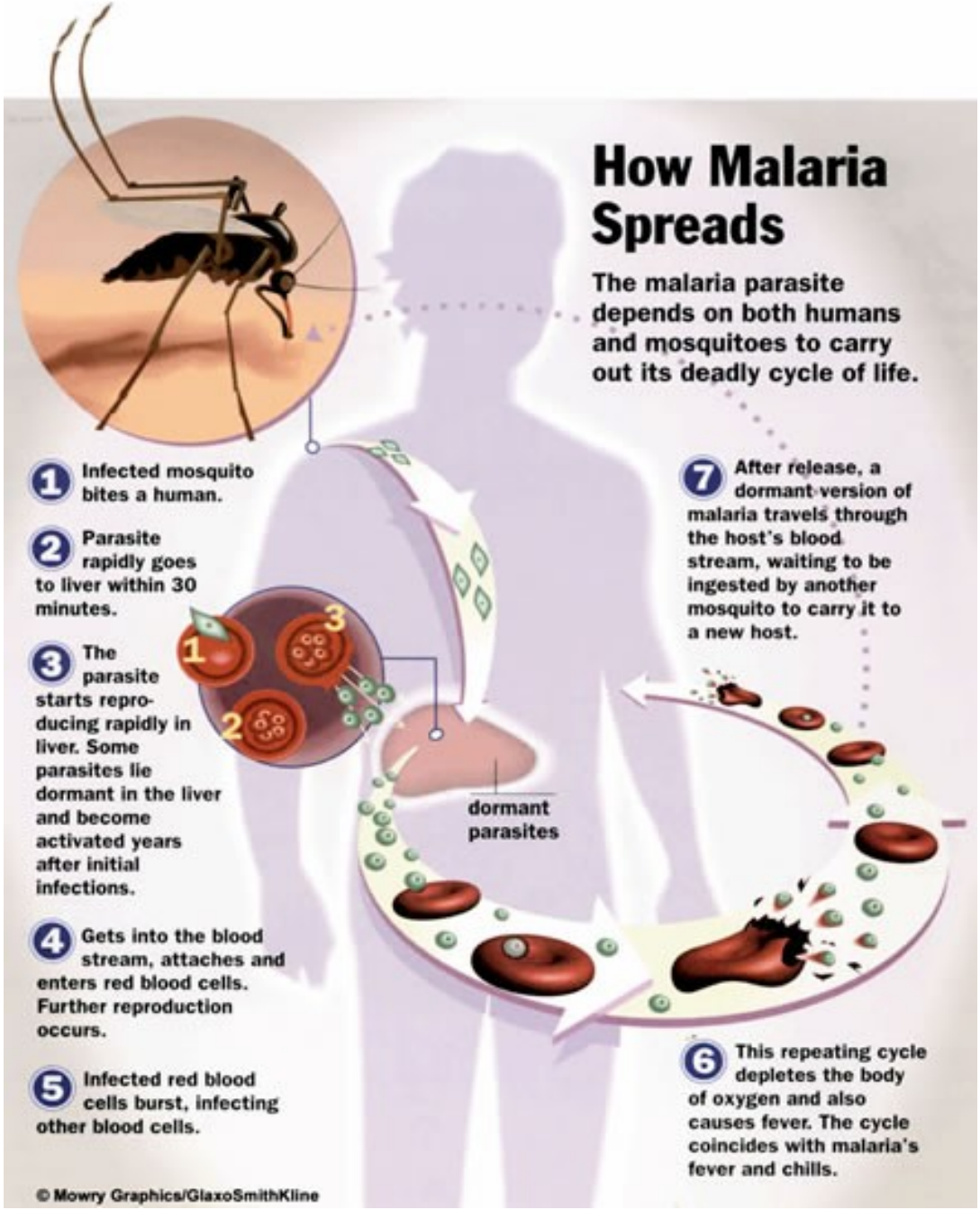
- rural areas
- standing waters
- occurrence outside urban agglomerations
- malaria does not occur in large cities, exception Mumbai (*A. stephansi*)

Pathogenesis of Malaria - Plasmodium has a wildly




Sporozoites penetrate human liver
Liver
In liver and lymphatic system
Sporozoites develop into merozoites
In liver


Sporozoites develop into merozoites
In liver
Gametocytes
Some merozoites invade the bloodstream
In red blood cells (48-hour cycle)
Merozoites develop into gametocytes

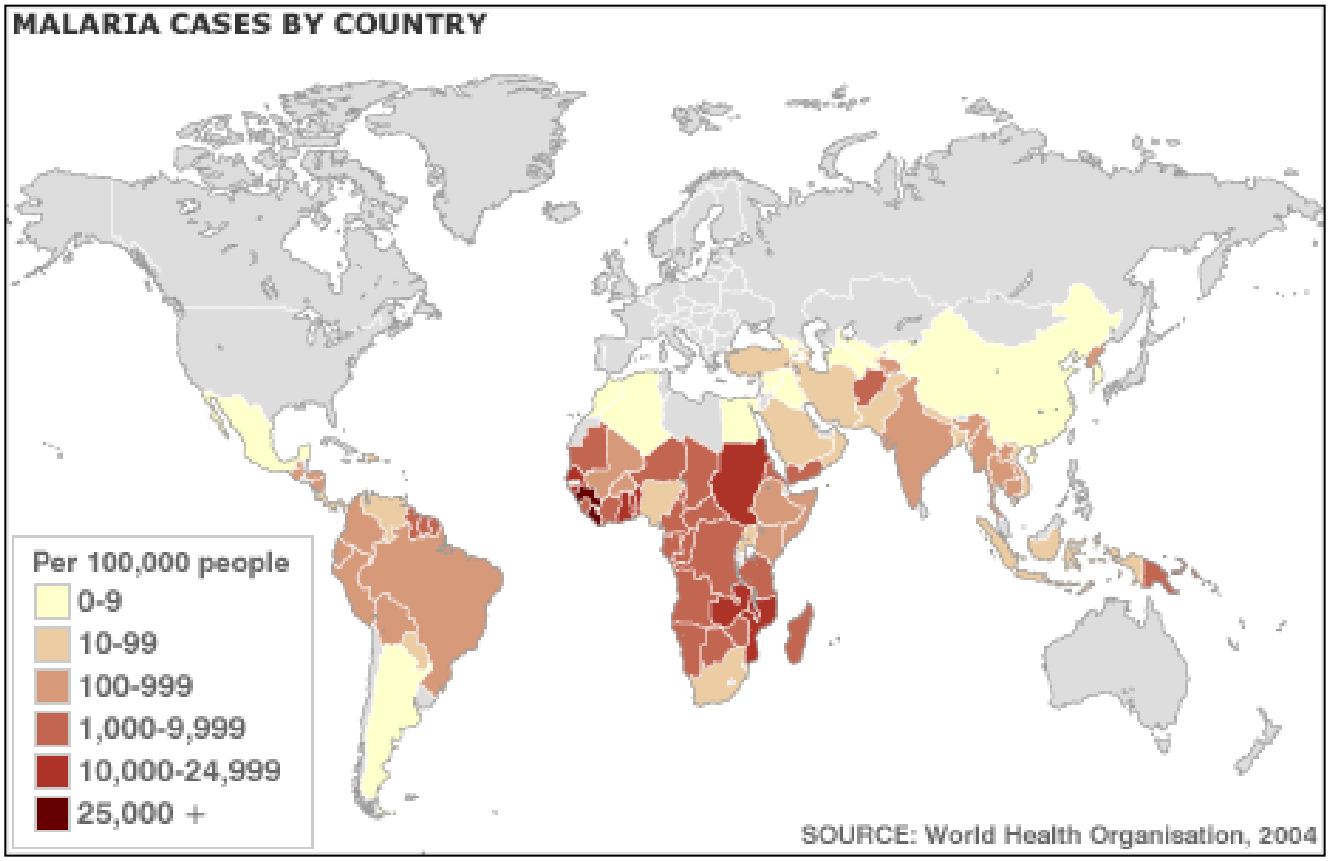

How Malaria Spreads
The malaria parasite depends on both humans and mosquitoes to carry out its deadly cycle of life.
1 Infected mosquito bites a human.
2 Parasite rapidly goes to liver within 30 minutes.
3 The parasite starts reproducing rapidly in liver. Some parasites lie dormant in the liver and become activated years after initial infections.
4 Gets into the blood stream, attaches and enters red blood cells. Further reproduction occurs.
5 Infected red blood cells burst, infecting other blood cells.
6 This repeating cycle depletes the body of oxygen and also causes fever. The cycle coincides with malaria's fever and chills.
7 After release, a dormant version of malaria travels through the host's blood stream, waiting to be ingested by another mosquito to carry it to a new host.
dormant parasites
© Mowry Graphics/GlaxoSmithKline

Distribution of Malaria

2.1 billion people live in MALARIOUS areas!

World Malaria Map by CDC

Like HIV and TB, malaria is unequally distributed, even in the tropics…



In areas of Africa with high transmission there are 2700 deaths per day = 2 per minute.

It’s especially hard on kids...

75% of the deaths are among African children!

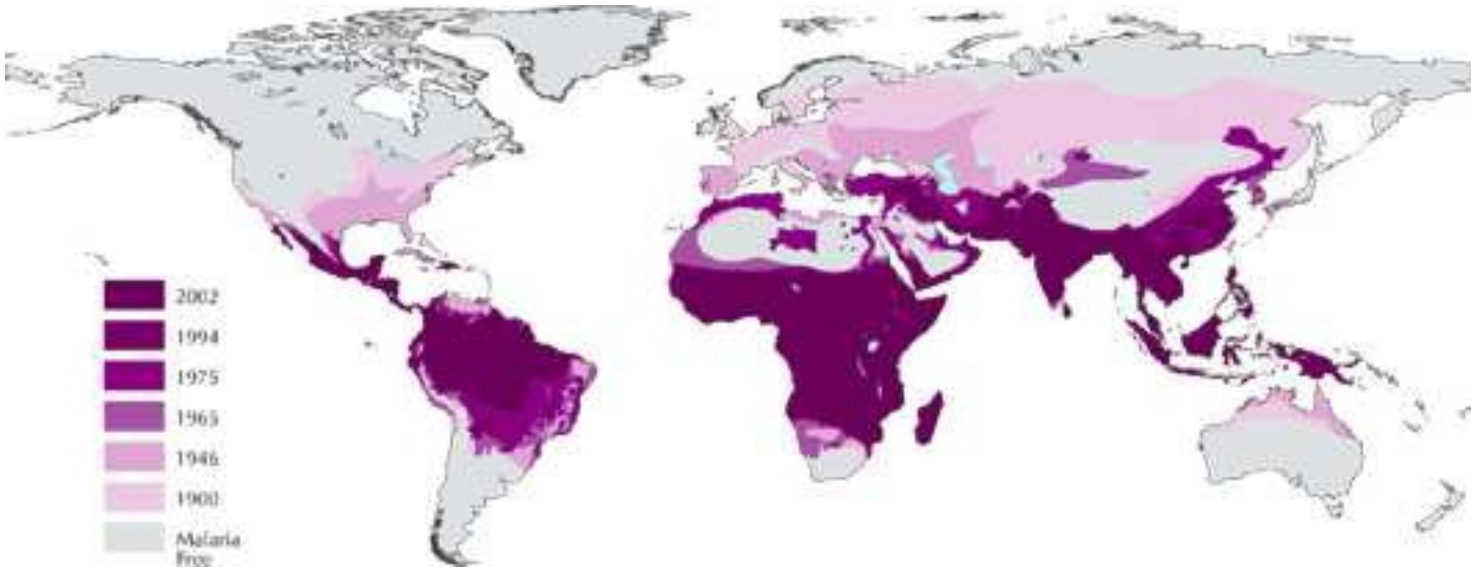
Leading Causes of Death in Children Under Five, for 2000-03 (WHO)

Rank	Cause	Numbers (x1000/year)	% of all deaths
1	Neonatal causes	3,910	37
2	Acute respiratory infections	2,027	19
3	Diarrheal diseases	1,762	17
4	Malaria	853	8
5	Measles	395	4
6	HIV/AIDS	321	3
7	Injuries	305	3
	Other causes	1,022	10
	Total	**10,596**	**100.0**

Geographic Occurrence of Malaria

- Malaria is found in tropical and subtropical regions, where Plasmodia may reproduce sexually
- Malaria does not occur in the mountains at altitudes above 1500 m, in equatorial areas over 2,500 m

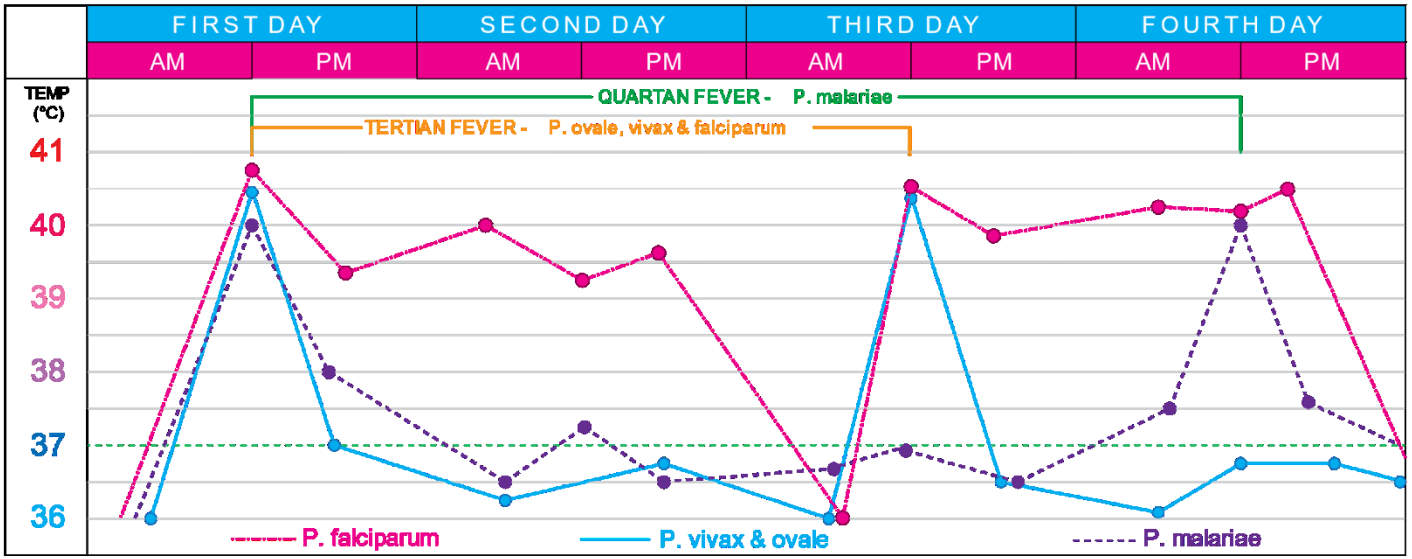
Historical Malaria Extension - the last case in Czechoslovakia in 1958



Malaria

Symptoms

- Initial non-specific symptoms: fever with headache, nausea, joint and muscle pain ("flu-like")
- Malaria attack - begins with a fever, chills, rapid rise of temperature to 40 ° C, fever lasts 2 to 12 hours, rapidly decreases, with markedly sweating
- Between attack of fever - growing fatigue, nausea, vomiting, diarrhea, dry cough...
- Objectively typically subikterus, hepatosplenomegaly
- Malaria is not accompanied by lymphadenopathy or exanthema



Severe Tropical Malaria (malignant)

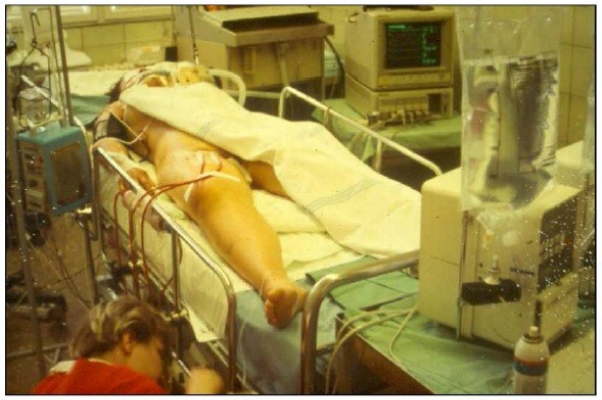
- *P. vivax* et *ovale* → attac only the young erythrocytes (reticulocytes)
- *P. malariae* → attac only older erythrocytes, parasitemia remains low
- *P. falciparum* (+ *knowlesi*) → attacks erythrocytes of various ages → high parasitemia

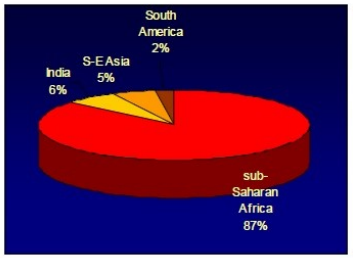
  On the surface of cells infected with *P. falciparum* occurs specifics adhesive molecules, lead to adhesion to capillary endothelium, infected cells accumulate in microcirculation of the CNS, kidney, liver, lung, myocardium → microtrombies, ischemia, DIC

- The lethality of the tropics imported is around 1%, in malignant forms up to 20%

Complications of tropical malaria:

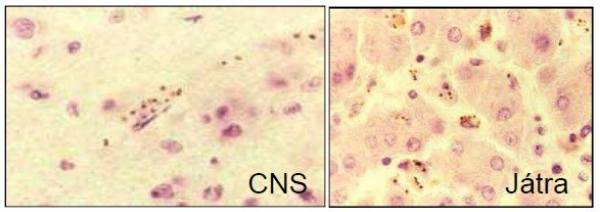
- Cerebral malaria
- Renal failure
- Pulmonary edema
- Bleeding symptoms
- Hepatic failure
- Gastrointestinal complications
- Circulation failure - algal malaria
- Hypoglycemia, ionic dysbalance...





87% případů tropické malárie je do ČR importováno ze subsaharské Afriky

Zdroj NRL, dr. E. Nohýnková



Cerebrální malárie s multiorgánovým selháním

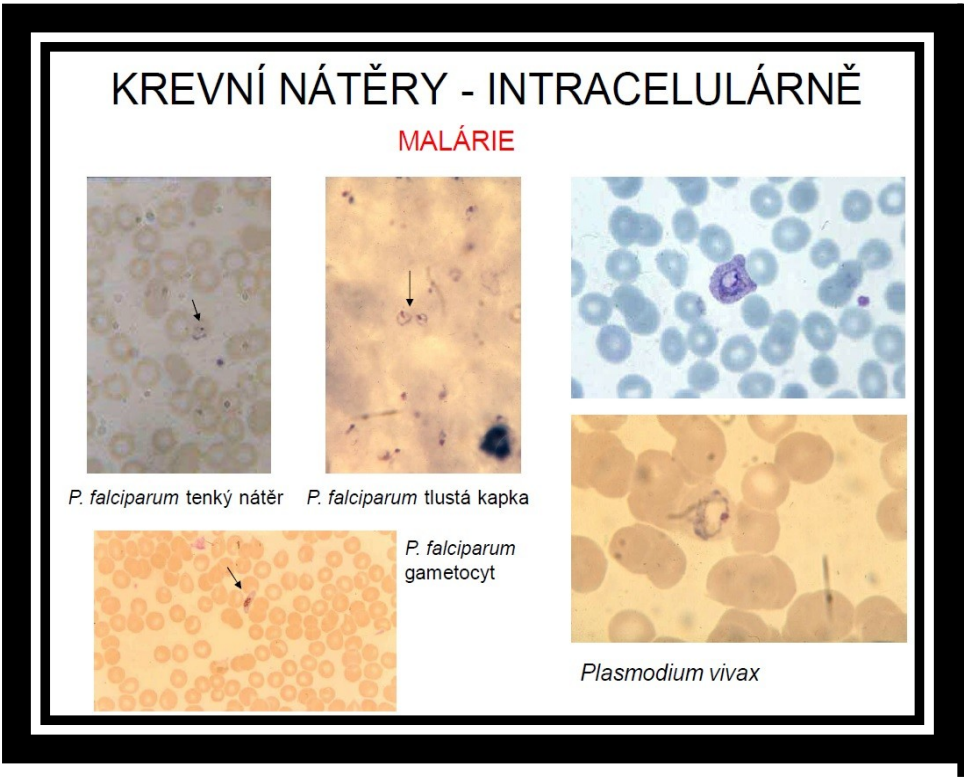
Clinical and Biological Criteria for Severe Malaria

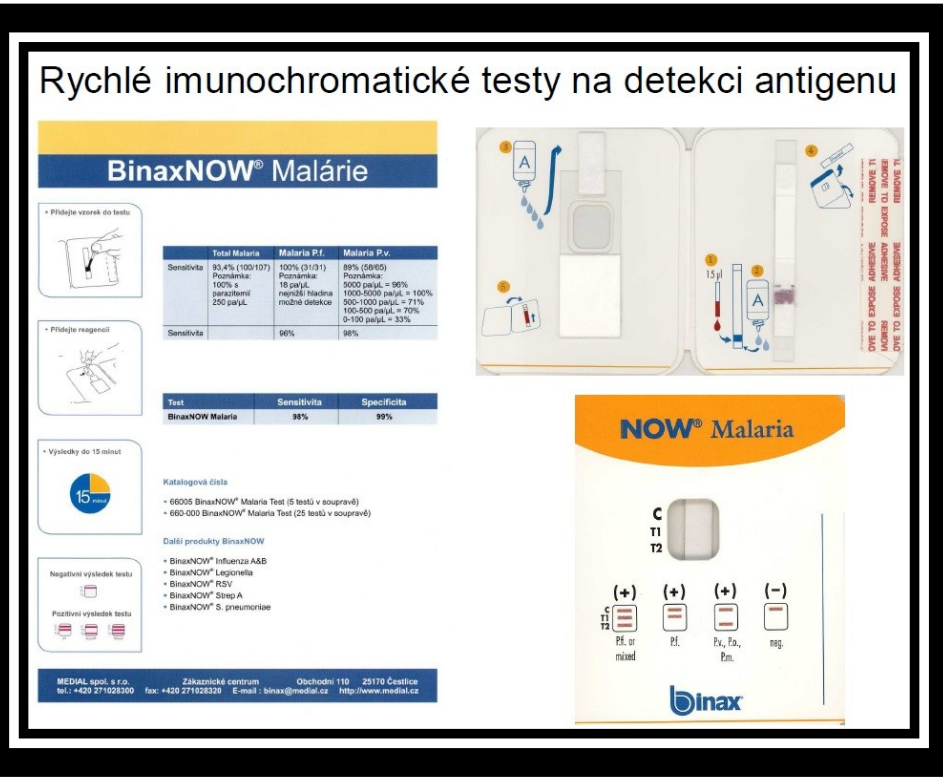
Clinical criteria
Impaired consciousness: Glasgow Coma Scale score <11*
Respiratory distress: requirement for noninvasive and/or endotracheal mechanical ventilation or spontaneous breathing with PaO_2 <60 mm Hg (if FiO_2 ≥0.21) †, and/or respiratory rate >32/min*
Multiple convulsions
Circulatory collapse: systolic blood pressure <80 mm Hg despite adequate volume repletion
Abnormal bleeding
Jaundice: clinical jaundice or bilirubin >50 µmol/L
Macroscopic hemoglobinuria: if unequivocally related to acute malaria (patients with blackwater fever were not included)
Laboratory criteria
Severe anemia: hemoglobin <5 g/dL
Hypoglycemia: blood glucose <2.2 mmol/L
Acidemia (pH<7.35) or acidosis (serum bicarbonate <15 mmol/L)
Hyperlactatemia: arterial lactate >5 mmol/L
Hyperparasitemia ≥4%
Renal impairment: serum creatinine >265 µmol/L or blood urea nitrogen >17 mmol/L*

*Coma scale criteria of 11 instead of 9; respiratory rate >32/minute and blood urea nitrogen > 17 mmol/L are modifications according to the SEAQUAMAT group [8].
†The requirement for noninvasive and/or endotracheal mechanical ventilation or spontaneous breathing with PaO_2 <60 mm Hg (if FiO_2 ≥0.21) was used specifically for this study.
doi:10.1371/journal.pone.0013236.t001

Diagnostic Tests for Malaria

- Thick and thin blood smears are gold standard
  - identify species and quantify density
- DNA probe, immunoassay





Differential Diagnosis of Malaria

- Dengue fever and others arbovirosis (rash)
- Typhoid fever
- Returnable typhus
- Rickettsiosis (rash)
- Leptospirosis (Southeast Asia)
- Septic states such as meningococcal sepsis (Africa)
- African trypanosomosis
- Schistosomiasis, filariasis (eosinophilia)
- Enteroviral infections
- Infectious mononucleosis – EBV, CMV (tonsilitis)
- Babesiosis
- Anaplasmosis
- Viral gastroenteritis (children, diarrhea)

Malaria Treatment

1) Targeted antimalarial therapy

Choice of antimalarial - depending on the type of plasmodium, the amount of parasitemia, the area of infection (incidence of antimalarial resistance) and the clinical condition of the patient

2) Supportive therapy

- for imported malaria always hospitalization, outpatient treatment - for semi-immune persons only
- for malignant malaria - complex intensive care (ICU), for cerebral malaria anti-edema therapy, corticosteroid effect controversial, currently not recommended

The success of treatment is monitored daily examination of blood smears until the disappearance of asexual stages.

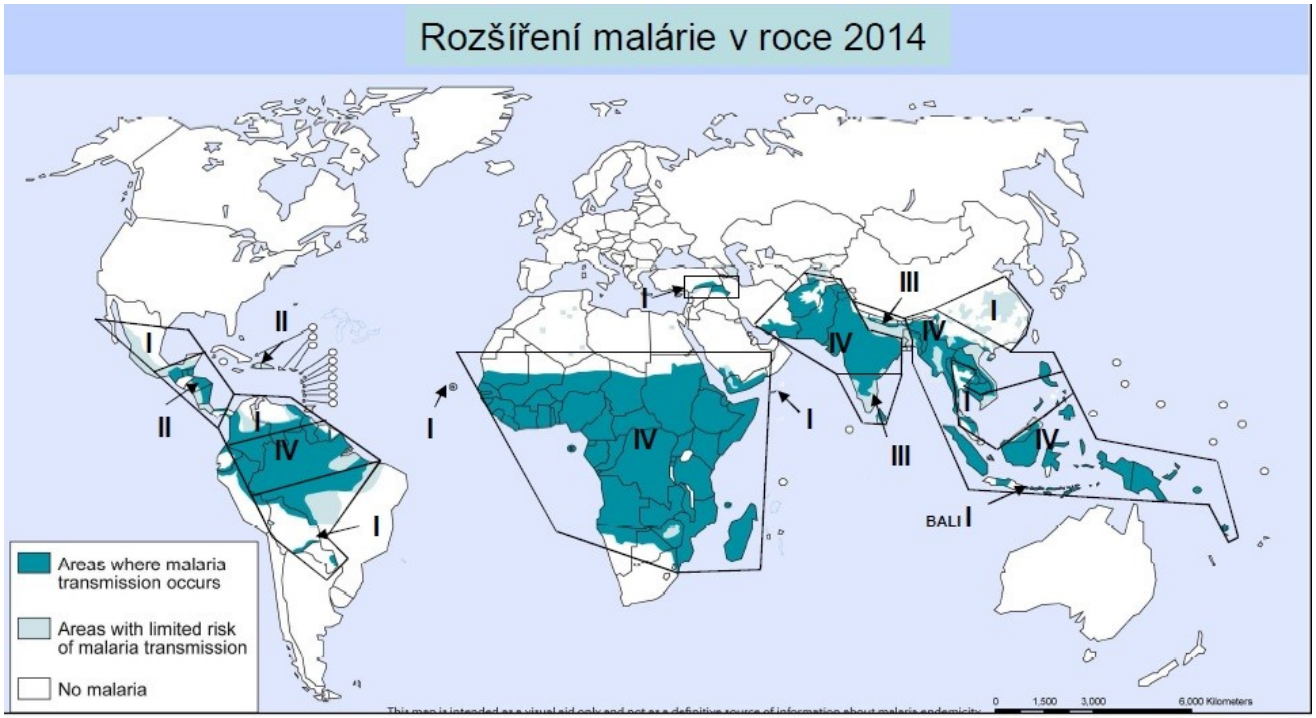
	Side effects	Contraindication	Availability
Chlorochin	GI SE	Alergy, epilepsy, porfyria, myastenia gravis	Plaquenil
Artemeter /lumefantrin	**GI SE**	**Alergy, first trimester of pregnancy**	**Riamet**
Atovachon /proguanil	**GI SE**	**Alergy, renal failure, pregnancy**	**Malarone**
Meflochin	Cardiotoxicity – arytmia sleeping disorders, nightmares	Alergy, epilepsy, depresiv disorders, schizophrenia, first trimester of pregnancy	Lariam
Chinin per os	Cardiotoxicity – arytmia Intervalu, cinchonism		only magistraliter
Chinin i.v.	**Cardiotoxicity – arytmia Intervalu, cinchonism**		**only magistraliter**
Primachin		**Alergy, deficiency of G6-PDH, pregnancy**	**Primaqiune**
Doxycyklin	**GI SE, photosensitivity**	**Alergy, liver disorders, pregnency, children under 6 years**	**ATB**

Prevention of Malaria

1) Personal Protection:

- protective clothing, **insect repellants**, household insecticide products
- window and door screens, bed nets

2) Antimalarial Chemoprophylaxis:



I – bez chemoprofylaxe

II – chlorochin

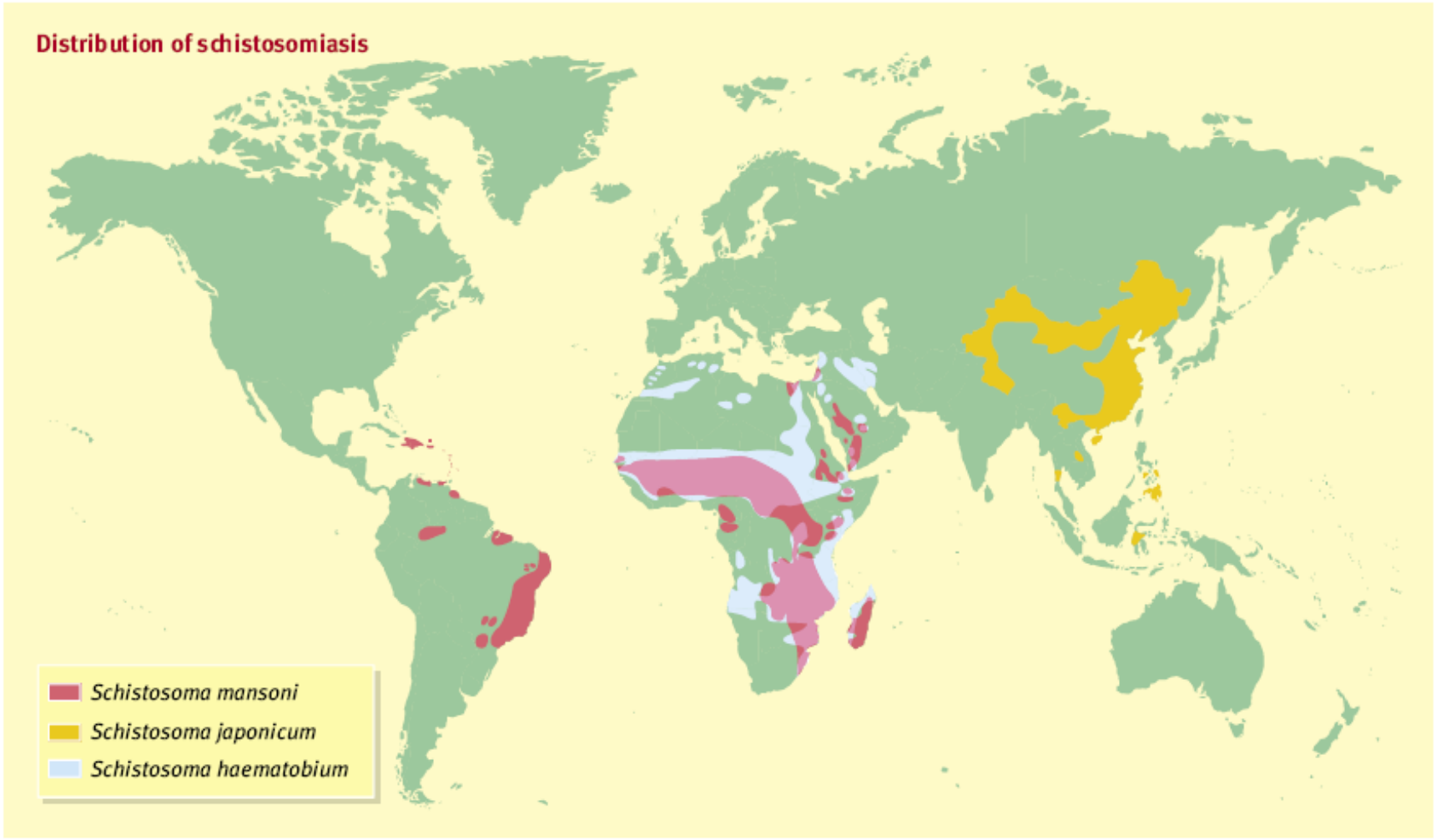
III – chlorochin + proguanil

IV – meflochin, Malarone (A/P), doxycyklin

Schistosomiasis

- **Parasitic disease** caused by several species of flatworm
- Affects many in **developing countries** (it's estimated that 207M have the disease and that of those, 120M are symptomatic)
- Can contract it by wading or swimming in lakes, ponds and other bodies of water infested with the parasite's snail host.

Distribution Map



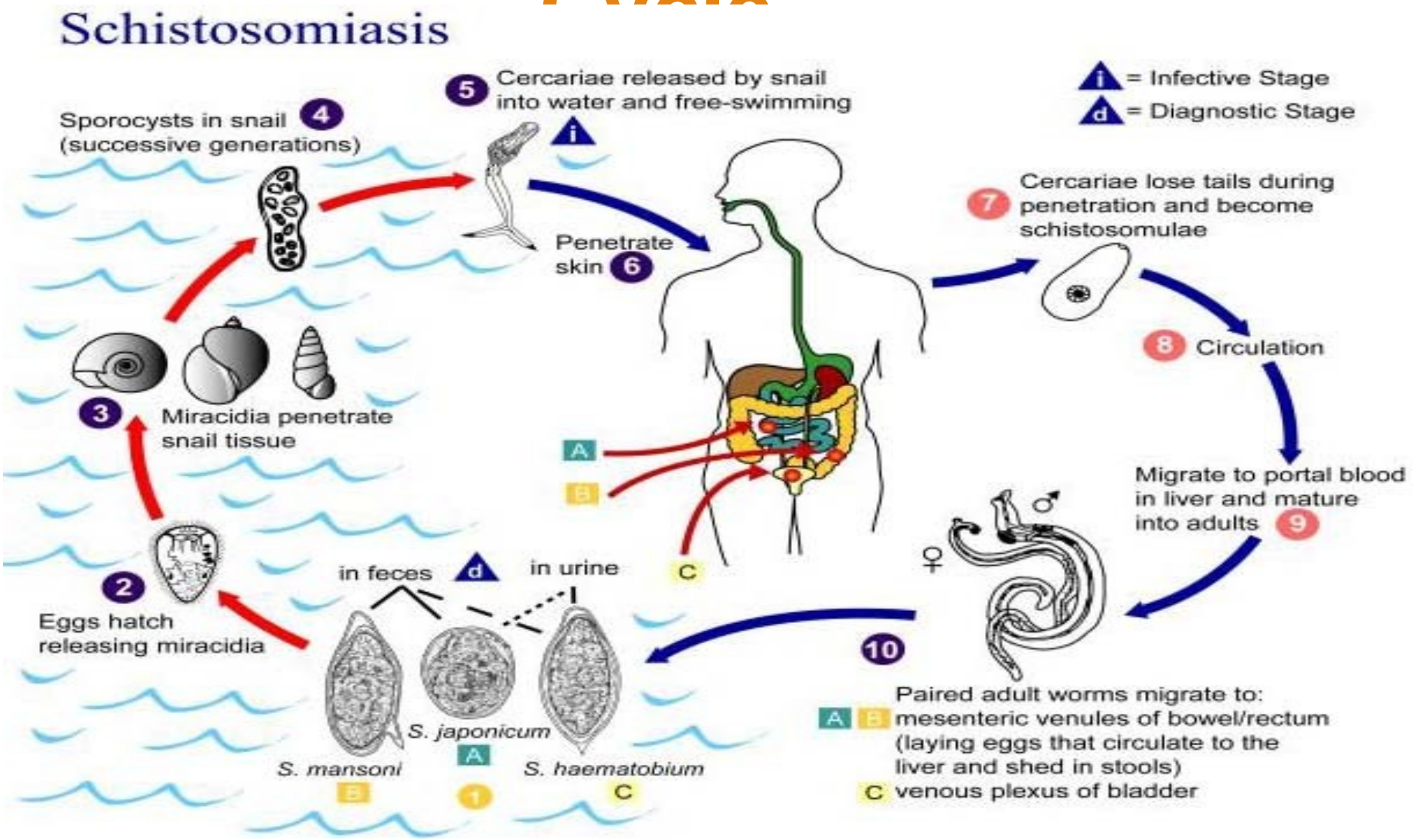
A Brief History...

- First described by German pathologist
- Theodore **Maximilian Bilharz**
- Bilharz performed autopsies on Egyptian patients who had died from the disease:

found male & female parasite eggs in the liver portal system, bladder.

- Later seen in Japan, called **Katayama fever**
  - *Symptoms: rash on legs, fever, diarrhoea, bloody stools → emaciation, edema → death.*

Life Cycle


Schistosomiasis
i = Infective Stage
d = Diagnostic Stage
5 Cercariae released by snail into water and free-swimming
i
Sporocysts in snail 4
(successive generations)
Penetrate skin 6
7 Cercariae lose tails during penetration and become schistosomulae
8 Circulation
3 Miracidia penetrate snail tissue
A
B
C
Migrate to portal blood in liver and mature into adults 9
♂
♀
in feces
d
in urine
2 Eggs hatch releasing miracidia
10
Paired adult worms migrate to:
A B mesenteric venules of bowel/rectum (laying eggs that circulate to the liver and shed in stools)
C venous plexus of bladder
S. japonicum
A
S. mansoni
B
S. haematobium
C
1

Life Cycle

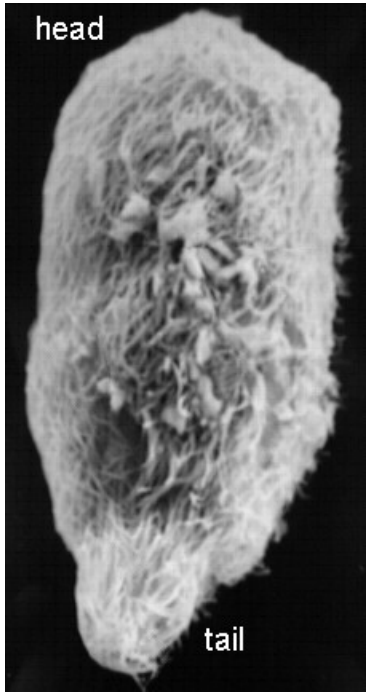
(eggs → larvae → snail)

1. Parasite eggs released **into freshwater** (from human urine, feces, blood)

2. Eggs hatch → **ciliated miracidia**, free swimming

3. Miracidia find & infect **snail host** (different species prefer different snail species)

4. Each miracidia transforms into many fork-tailed, free swimming forms called **cercariae** within 4-6 weeks of entering snail.



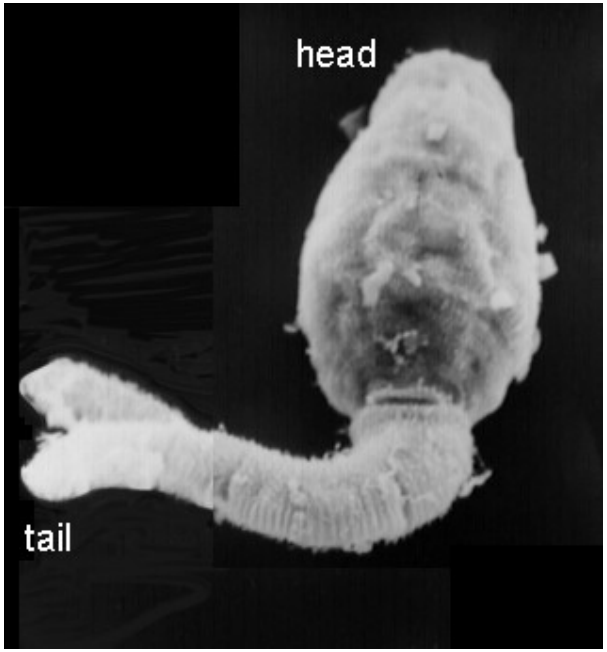
Miracidia larva with cilia

5. Cercariae **leave snail and move into water** at a rate of 1500/day for up to 18 days.

Life Cycle

(into human → lymphatics → lungs → liver)

6. Cercariae find a human host, penetrate skin, and differentiate into larval forms called **schistosomulae**.



Cercariae with forked tail

7. Migrate through the host's skin, gain access to the lymphatic system.

8. Travel to the lungs (stay 3-8 days, 70% are eliminated)

9. Migrate to liver portal system, mature into male & female adults

Life Cycle

(maturation → movement to target organs → egg production)

10. In liver m & f pair up → female inserts herself into the **gynecophoral canal** of male

Paired male & female

11. Migrate to favoured sites:

S. mansoni – mesenteric venules of large bowel & rectum

S. japonicum – mesenteric veins of the small intestine

S. haematobium – perivesical venous plexus surrounding the bladder

Life Cycle

(eggs release)

12. Females release **eggs**

Egg characteristics:

- covered in microbarbs → cling to vascular endothelium

- pores, which allow the release of:

    1) Antigens
    2) Enzymes (aid in passage of eggs through host tissues)

13. Eggs enter lumen of excretory organs

50% → passed out of body (urine, stool, blood)
50% → trapped in tissues

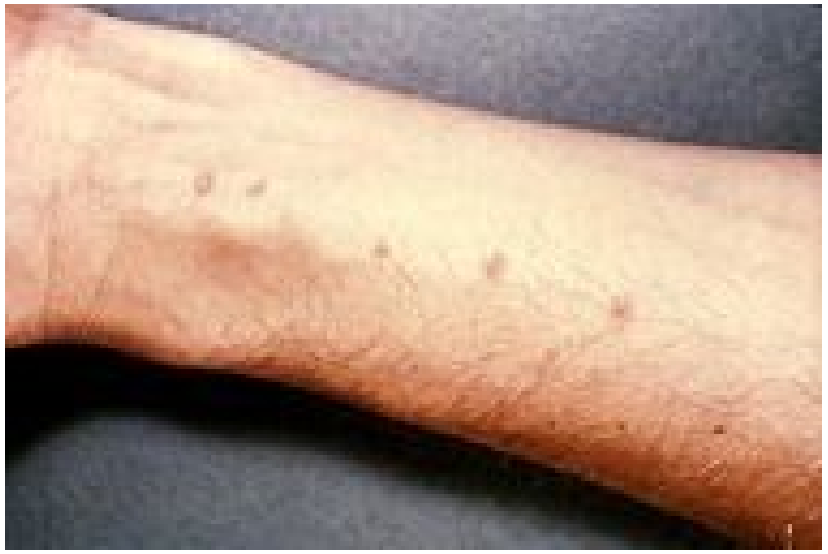
Acute Infection

(early stage)

- Cercariae penetrate skin → **rash** (schistosome or swimmer's itch)
- Eggs laid in target organs release antigens

Cause Katayama fever:

- *fever*
- *eosinophilia*
- *urticaria*
- *malaise*
- *diarrhea*



Chronic Infection

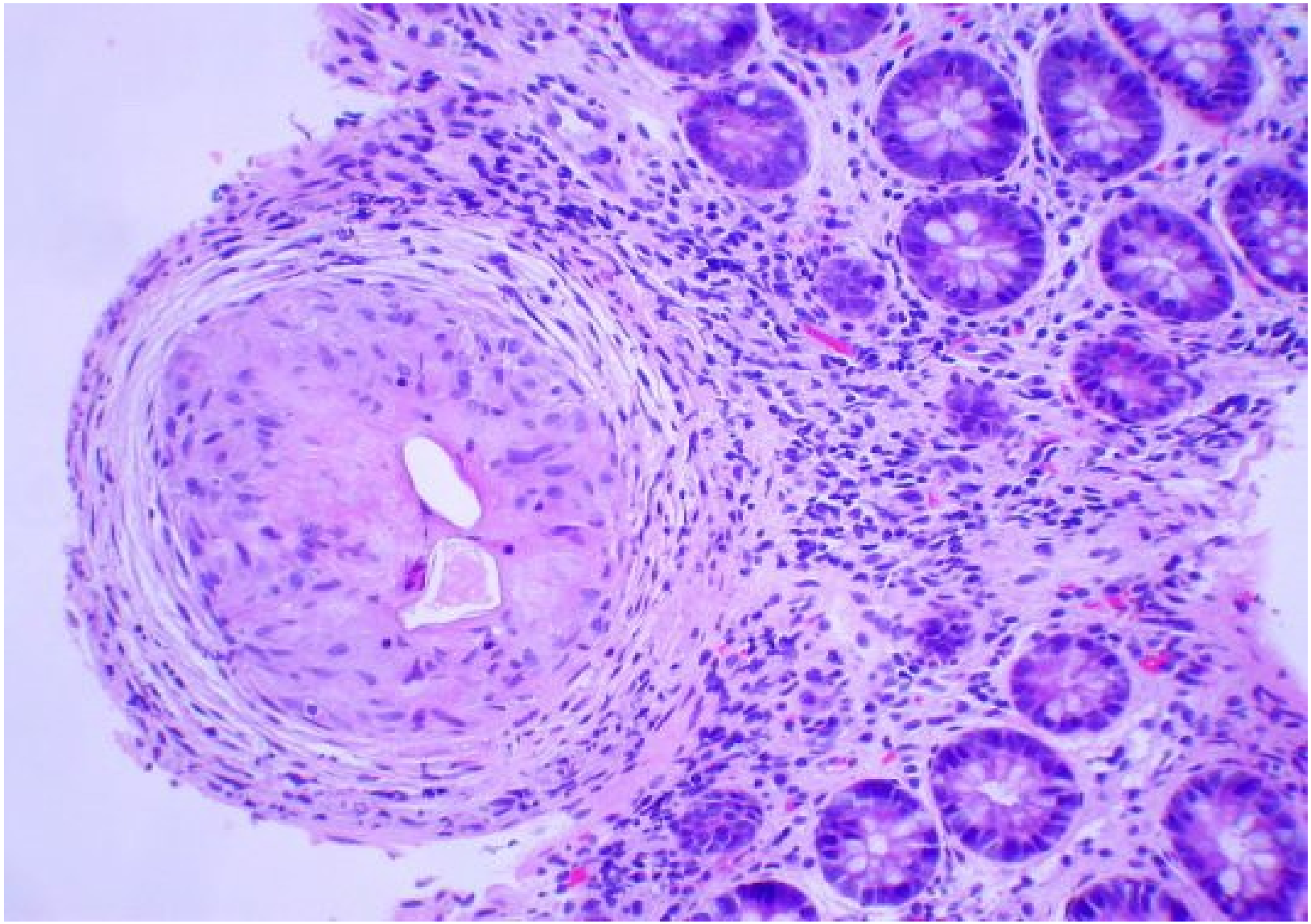
Symptoms of chronic infection (late stage) **caused by eggs that travel to various parts of body**

Eggs remain trapped in host tissues → **secrete Ags** → **granulomatous inflammatory immune response**

Fibroblast cells are also at site of Infection. During late stage of chronic infection, they replace the granulomas. Their prolif. is stim. by factors produced by the schistosome egg and by cytokines from macrophages and CD4 T-cells.

Fibroblasts mediate collagen deposition in the granuloma, leading to **fibrosis (= fibrous connective tissues development).**

Granulo



Chronic Infection

(when eggs meet the GI tract)

In *Schistosoma mansoni* infections:

Wall of **colon is damaged** as eggs pass through inflamm. response → ulcers, inflammatory polyps, lead to fibrosis

- Clinically: **diarrhea, abdominal pain**
- Eggs can also accumulate in the appendix
  - can lead to **appendicitis**

Chronic Infection

- **Hepatosplenic schistosomiasis** (when eggs meet the liver/spleen)
- Eggs carried by portal circulation → **liver**
- Granulomatous response
- Granulomas are walled off with fibrous tissue → fibrosis obstructs portal veins → **portal hypertension, liver cirrhosis**
  - esophageal varices (dilated esophageal veins, which drain the liver→ bursting can cause bleeding to death. Caused directly by portal hypertension.)
  - splenomegaly (enlarged spleen, due to fibrosis)…

Chronic Infection

- In those with severe hepatosplenic schistosomiasis (when eggs meet the heart)
- Blood gets **shunted directly back to the heart** (doesn't pass through liver).
- Eggs accumulate in heart, sometimes lodged in pulmonary arterioles.
- Form granulomas → block pulmonary circulation → pulmonary hypertension.
    - can lead to right ventricular failure, and eventually cardiovascular collapse.

Chronic Infection

(when eggs meet the genitourinary areas or CNS)

Genitourinary complications

- Eggs lodge themselves in wall of bladder & can develop into polyps
- Polyps can erode, ulcerate & cause hematuria (blood cells in urine)
- Eggs lodge in ureters and urethra, cause lumps and lesions → kidney failure
- Eggs lodge into ovaries, the uterus, cervix, fallopian tubes → **lumps → complications incl. infertility**

(For the men: eggs can also lodge into the testes and the prostate)

CNS complications

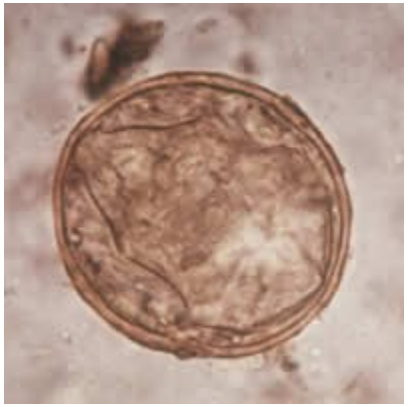
- *S. haematobium* and *S. mansoni* can migrate to the spine
- *S. japonicum* found in the brain and **causes encephalopathy** (general brain dysfunction)

Diagnosis

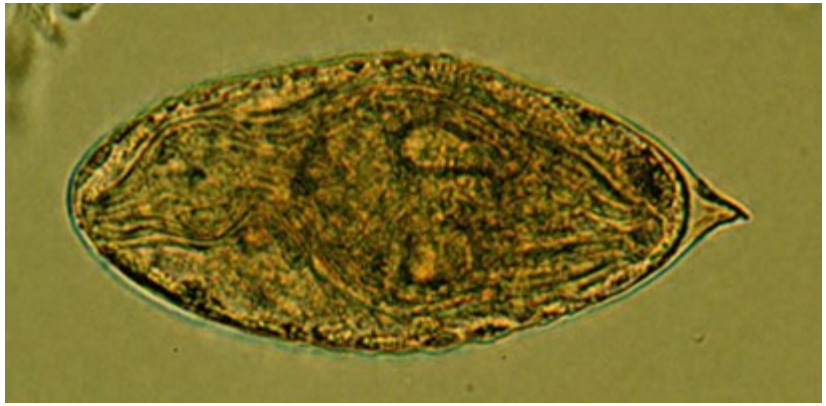
Microscopic Detection

- Take stool or urine sample to detect eggs
- *S. haematobium* eggs are oval and have a spike at the tip
- *S. japonicum* eggs small and almost spherical with tiny spine
- *S. mansoni* eggs have a spike on the side (spine)

S. mansoni



S. japonicum



S. haematobium

Diagnosis

Antibody tests

- An earlier and more sensitive form of detection
- Some complications
  - Cross-reactivity with other helminthic infections (other flatworm parasites)
  - Can't tell the difference between current and old infections as antibodies stay long after infection is over.
  - Can't tell you anything about overall worm burden so we can't tell how serious the infection is

Diagnosis

Antigen tests:

- Detect antigens in blood with immunoelectrophoresis
- 2 types are detected though share similar complications with antibody tests

Molecular detection:

- 20-25% of schistosomiasis genome has been sequenced → can use 2 probes to detect *S. mansoni* DNA in human blood
- Genome sequencing has the potential to yield DNA vaccines

Prevention

- For travelers it's easy - **don't swim in fresh, stagnant water** (running water is better, still not safe).

- Harder in endemic areas → people are d**ependent on nearby freshwater**.
- Focused on education, eliminating snail nesting grounds
- „Molluscicides" can be used to eliminate snails.
- **Proper irrigation systems and engineering are key**
- There are ways to build irrigation and canalization systems that don't allow snails to inhabit the surrounding area

  However, many irrigation/canalization projects since the 50s have ignored UN instructions, may have contributed to spread of the parasite!

Treatment

- Swimmer's itch and Katayama Fever are usually treated symptomatically.

- Chemotherapy is treatment of choice - **Praziquantel is most widely used drug.**

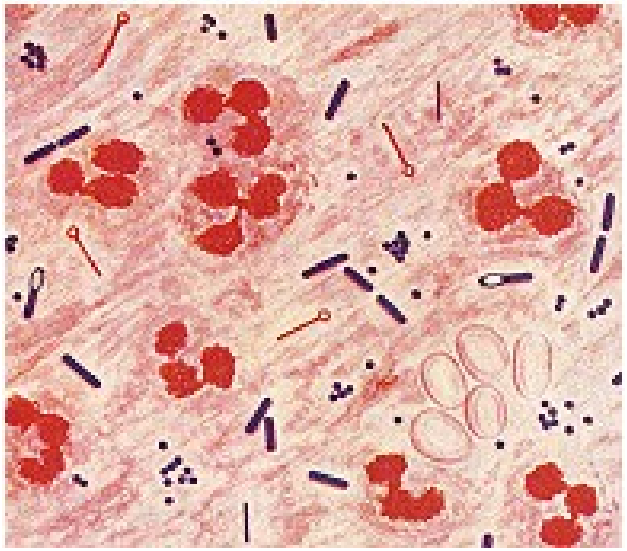
Praziquantel

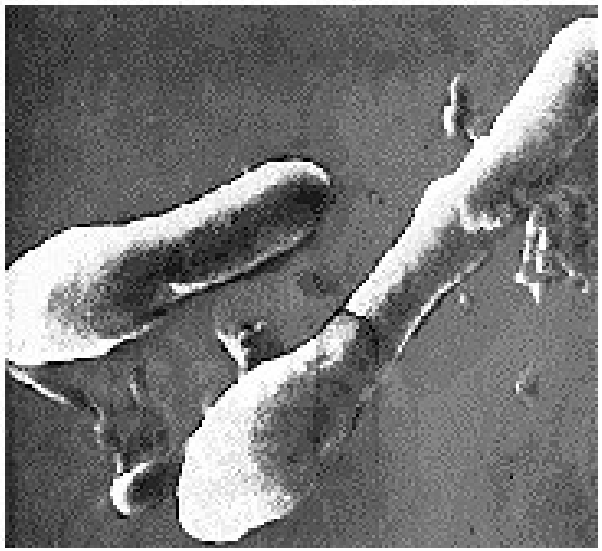
- Extremely well tolerated, few side effects
- Broad-spectrum antihelminthic drug (antihelminthic= drugs that expel parasitic worms)
- Cures schistosomiasis in 80 – 90% of patients, 90% reduction in egg excretion in those not cured
- Causes worm muscles contract – cannot hold onto human tissues
- **Resistance has been reported in Egypt and Senegal**

Tetanus

Clostridium tetani

- relatively large, Gram-positive, rod-shaped bacteria
- spore-forming, anaerobic
- found in soil, especially heavily-manured soils, and in the intestinal tracts and feces of human and animals





Left. Stained pus from a mixed anaerobic infection. At least three different clostridia are apparent.

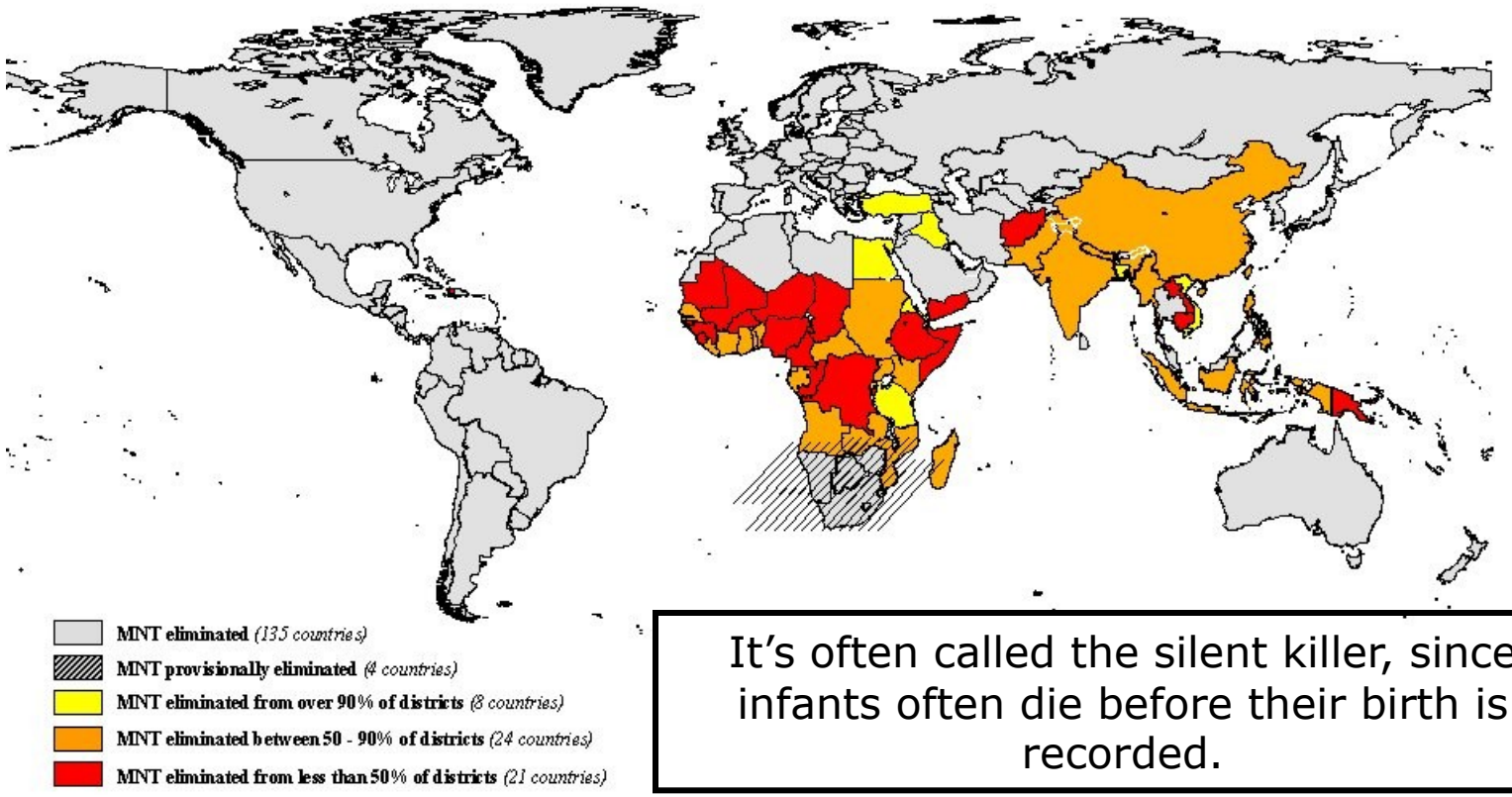
Right. Electron micrograph of vegetative *Clostridium tetani* cells.

Brief History of Disease

- 5th century BC: Hippocrates first **described** the disease
- 1884: Carle and Rattone discovered the **etiology** *(cause/origin of disease)*
  - Produced tetanus by injecting pus from a fatal human case
  - Nicolaier was able to do the same by injecting soil samples into animals
- 1889: Kitasato **isolated** the organism from human victim, showed that it could produce disease when injected into animals. Reported that **toxin** could be **neutralized** by specific antibodies.
- 1897: Nocard demonstrated the protective effect of **passively transferred antitoxin** → used in WWI
- 1924: Descombey developed tetanus toxoid for **active immunization** → used in WWII

Distribution

In developing countries, neonatal tetanus is a leading cause of neonatal mortality, accounting for over 250,000 deaths annually.

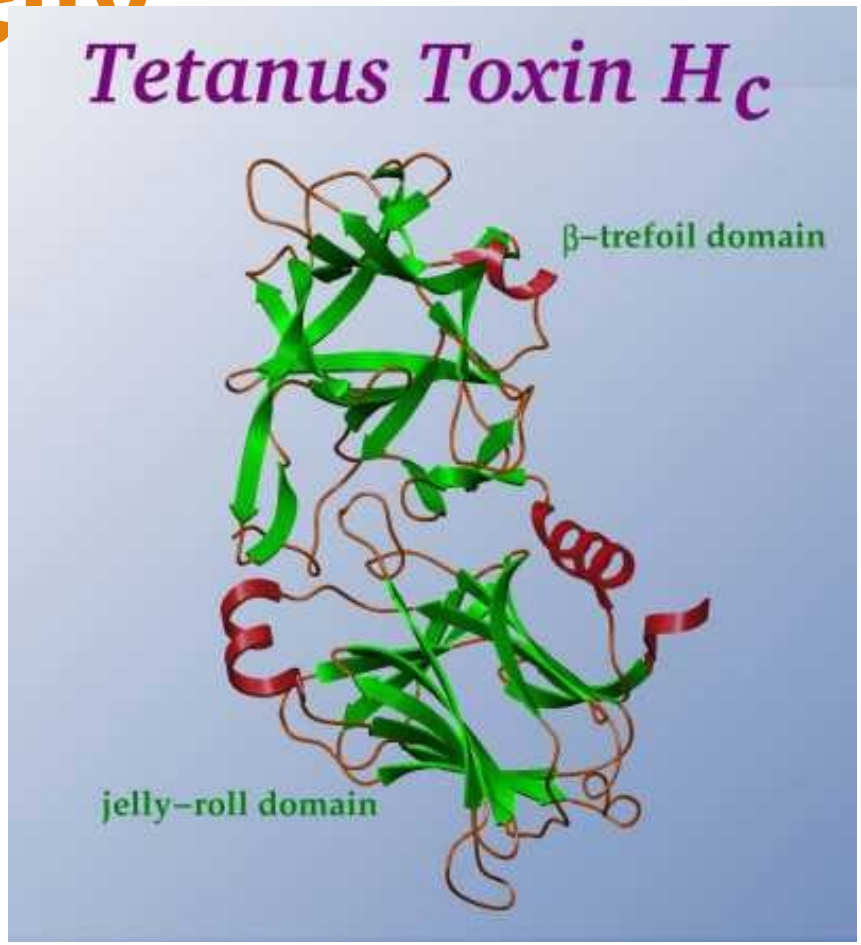


It's often called the silent killer, since infants often die before their birth is recorded.

Virulence & Pathogenicity

Not pathogenic to humans and animals by invasive infection but by the production of a potent protein toxin!

1. **Tetanus toxin** or **tetanospasmin**
2. The second exotoxin produced is tetanolysin (function not known)

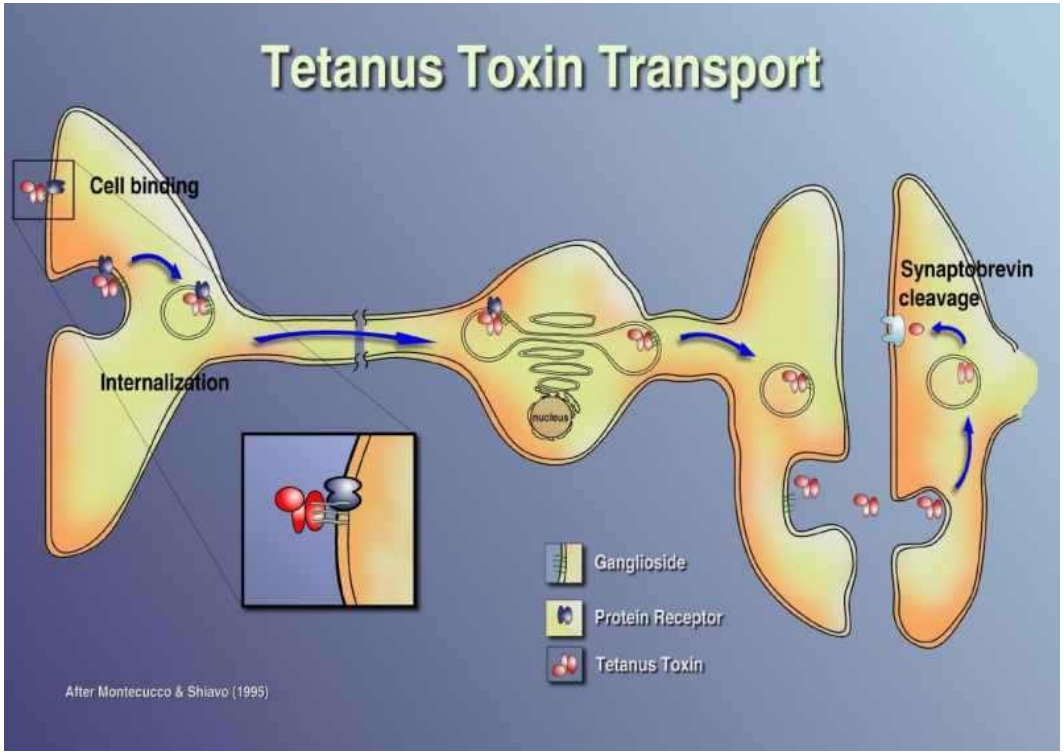


Tetanus toxin

- Produced when spores germinate and vegetative cells grow after gaining access to wounds. The organism multiplies locally and symptoms appear remote from the infection site.

- **One of the three most poisonous substances known on a weight basis**, the other two being the toxins of botulism and diphtheria.
  - Tetanus toxin is produced in vitro in amounts up to 5 to 10% of the bacterial weight.
  - Estimated lethal human dose of Tetanospamin = 2.5 nanograms/kg body

- Because the toxin has a specific affinity for nervous tissue, it is referred to as a **neurotoxin**. The toxin has no known useful function to *C. tetani*.



1. Initially binds to **peripheral nerve terminals**

2. Transported within the axon and **across synaptic junctions** until it reaches the central nervous system

Blocks the release of **inhibitory neurotransmitters** (glycine and gamma-amino butyric acid, GABA) across the synaptic cleft, which is required to check the nervous impulse.

If nervous impulses cannot be checked by normal inhibitory mechanisms, it leads to unopposed muscular contraction and spasms that are characteristic of tetanus.

Methods of Transmission

- *C. tetani* can live for years as spores in feces and soil. As soon as it enters the human body through a major or minor wound and the conditions are anaerobic, the spores germinate and release the toxins.

- Tetanus may follow burns, deep puncture wounds, ear or dental infections, animal bites, abortion.

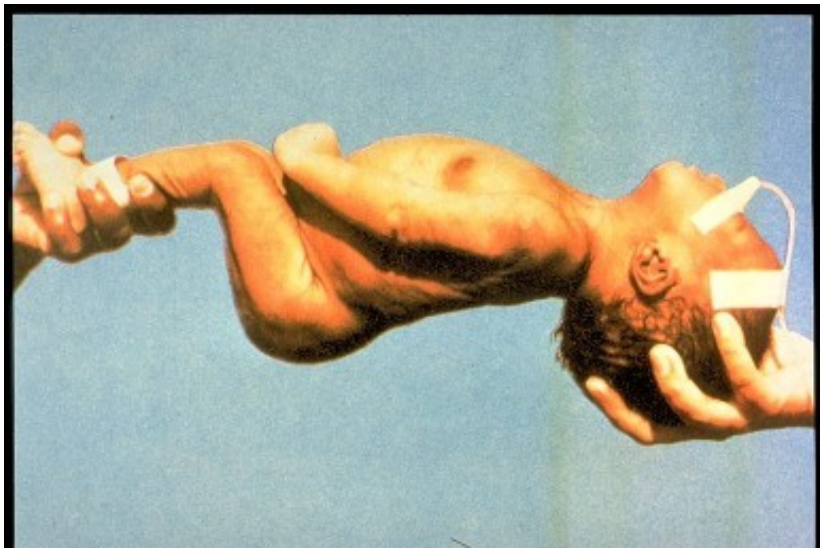
- Only the growing bacteria can produce the toxin.
- It is the only vaccine-preventable disease that is *infectious but not contagious* from person to person.

Symptoms

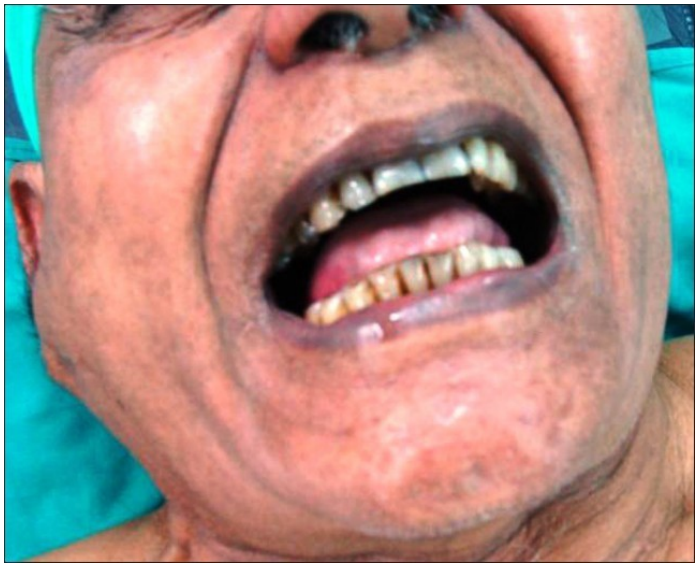
- **Tetanic seizures** (painful, powerful bursts of muscle contraction)
- if the muscle spasms affect the larynx or chest wall, they may cause asphyxiation
- stiffness of jaw (also called lockjaw)
- **stiffness of abdominal and back muscles (opisthotonus)**
- contraction of facial muscles (risus sardonicus)

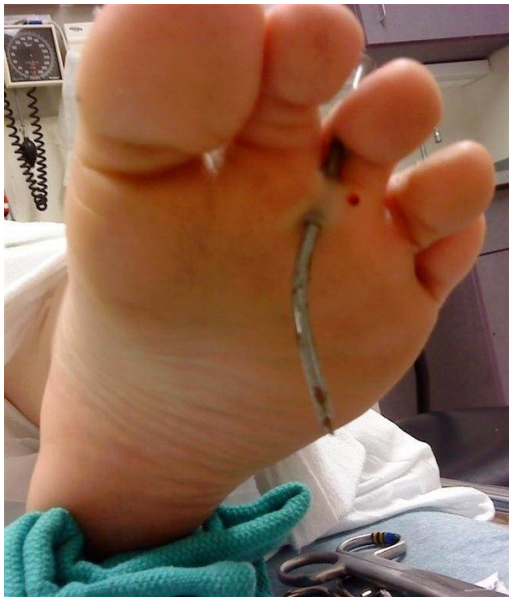
The back muscles are more powerful, thus creating the arc backward

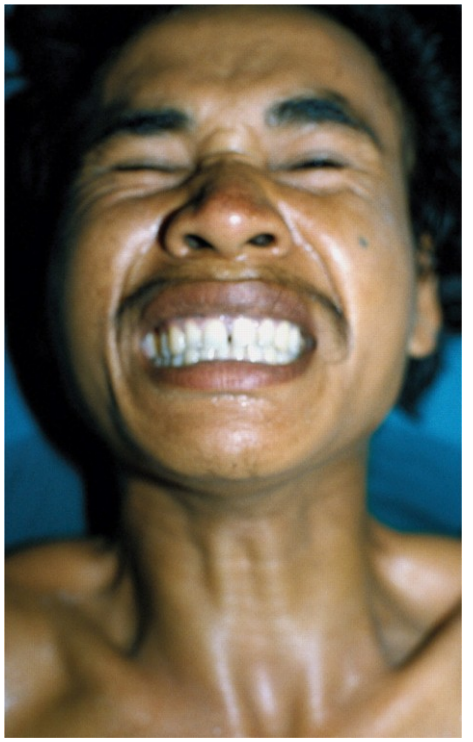
"Oposthotonus" by Sir Charles Bell, 1809.

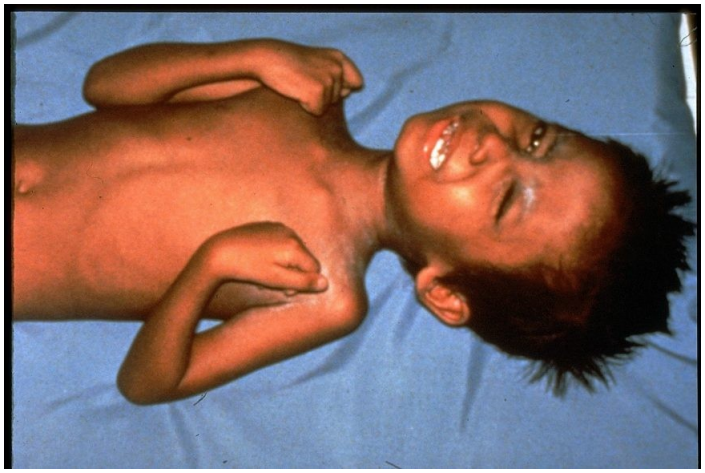


Baby has neonatal tetanus with complete rigidity









Most Common Types of Tetanus

Generalized tetanus

- descending pattern: lockjaw → stiffness of neck → difficulty swallowing → rigidity of abdominal and back muscles.
- spasms continue for 3-4 weeks, and recovery can last for months
- **death occurs when spasms interfere with respiration.**

Neonatal tetanus

- form of generalized tetanus that occurs in newborn infants born without protective passive immunity because the mother is not immune.
- usually occurs through infection of the unhealed umbilical stump, particularly when the stump is cut with an unsterile instrument.

Methods of Diagnosis

- based on the patient's account and physical findings that are characteristic of the disease

- diagnostic studies generally are of little value, as cultures of the wound site are negative for *C. tetani* two-thirds of the time

- Tests that may be performed include the following:
  - culture of the wound site (may be negative even if tetanus is present)
  - tetanus antibody test
  - other tests may be used to rule out **meningitis**, **rabies**, strychnine poisoning, or other diseases with similar symptoms

Clinical Treatment

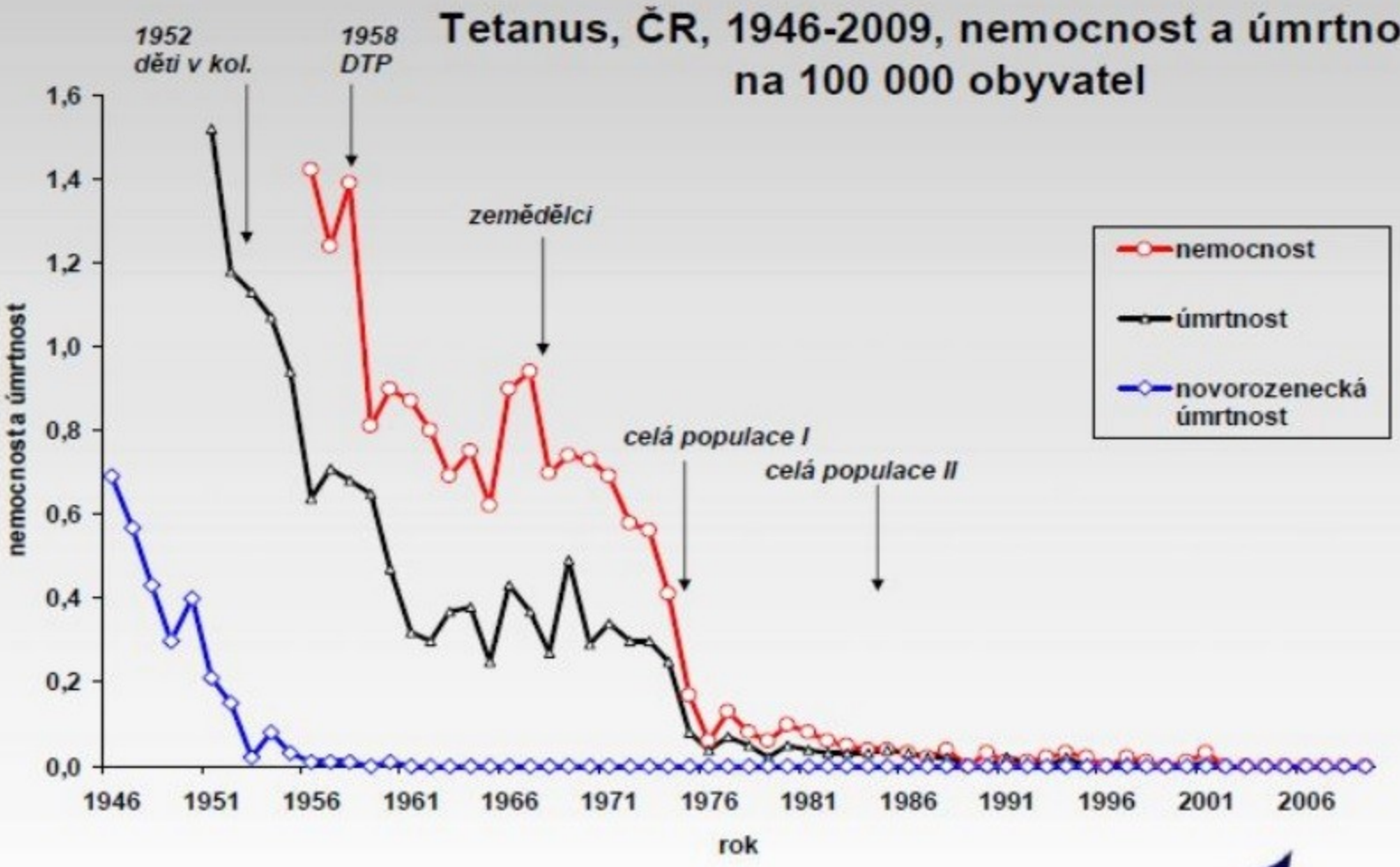
- if treatment is not sought early, the disease is often fatal
- the bacteria are killed with antibiotics, such as **penicillin** or **metronidazol**; further toxin production is thus prevented
- the toxin is neutralized with shots of **tetanus immune globulin, TIG**
- other drugs may be given to provide **sedation**, relax the muscles and relieve pain
- due to the extreme potency of the toxin, immunity does not result after the disease

Method of Prevention (immunization)

- A person recovering from tetanus should begin active immunization with tetanus toxoid (Td) during reconvalescence.
- The vaccine includes **tetanus toxoids** is routinely given in the EU during childhood. Because the antitoxin levels decrease over time, booster immunization shots are needed every 15 - 20 years.
- **Postexposure Prophylaxis:**

Previous doses of tetanus toxoid*	Clean and minor wound		All other wounds	
	Tetanus toxoid-containing vaccine[Δ]	Human tetanus immune globulin	Tetanus toxoid-containing vaccine[Δ]	Human tetanus immune globulin[◊]
<3 doses or unknown	Yes[§]	No	Yes	Yes
≥3 doses	Only if last dose given ≥10 years ago	No	Only if last dose given ≥5 years ago[¥]	No

Dopady očkování v ČR



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