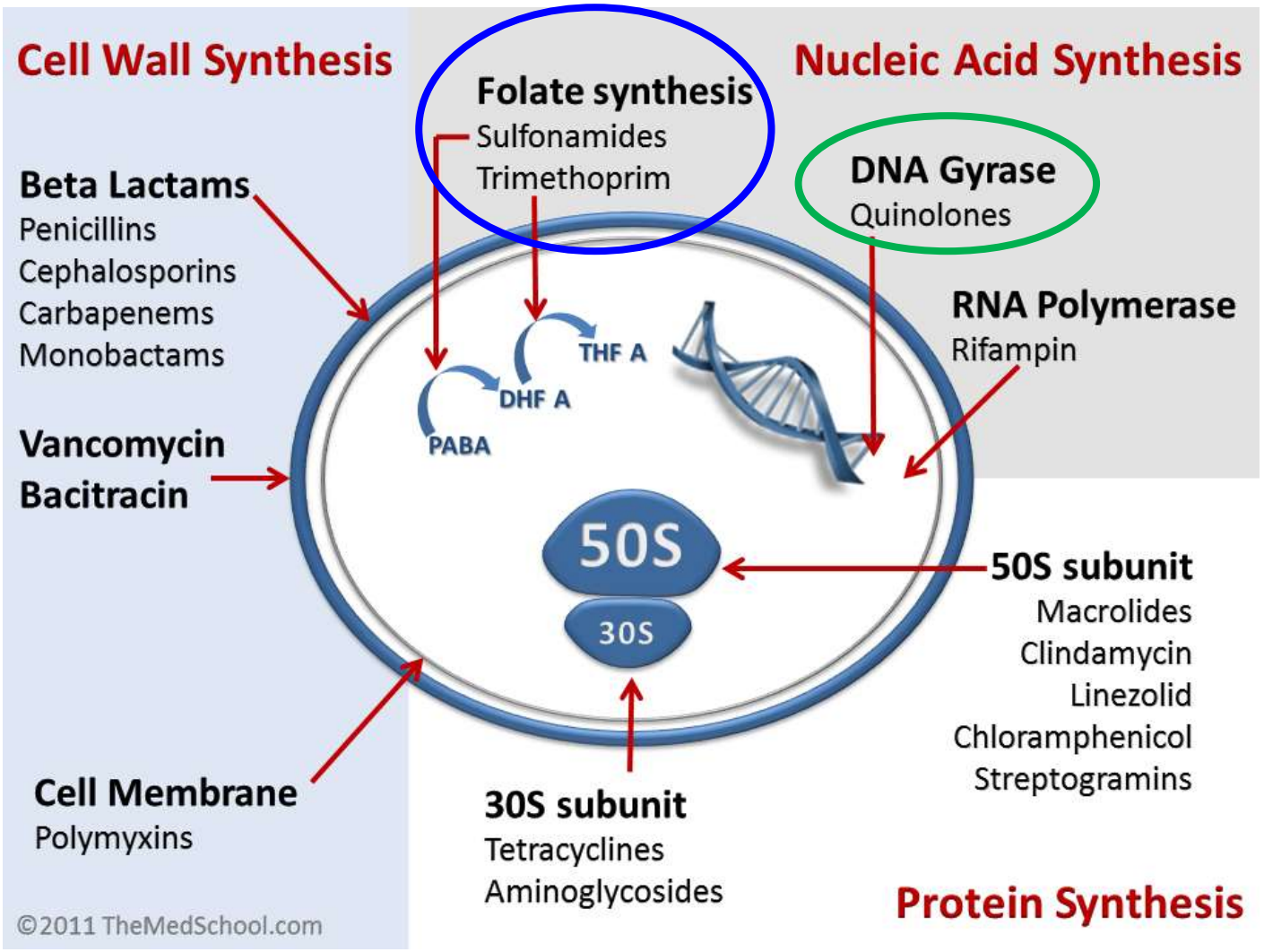
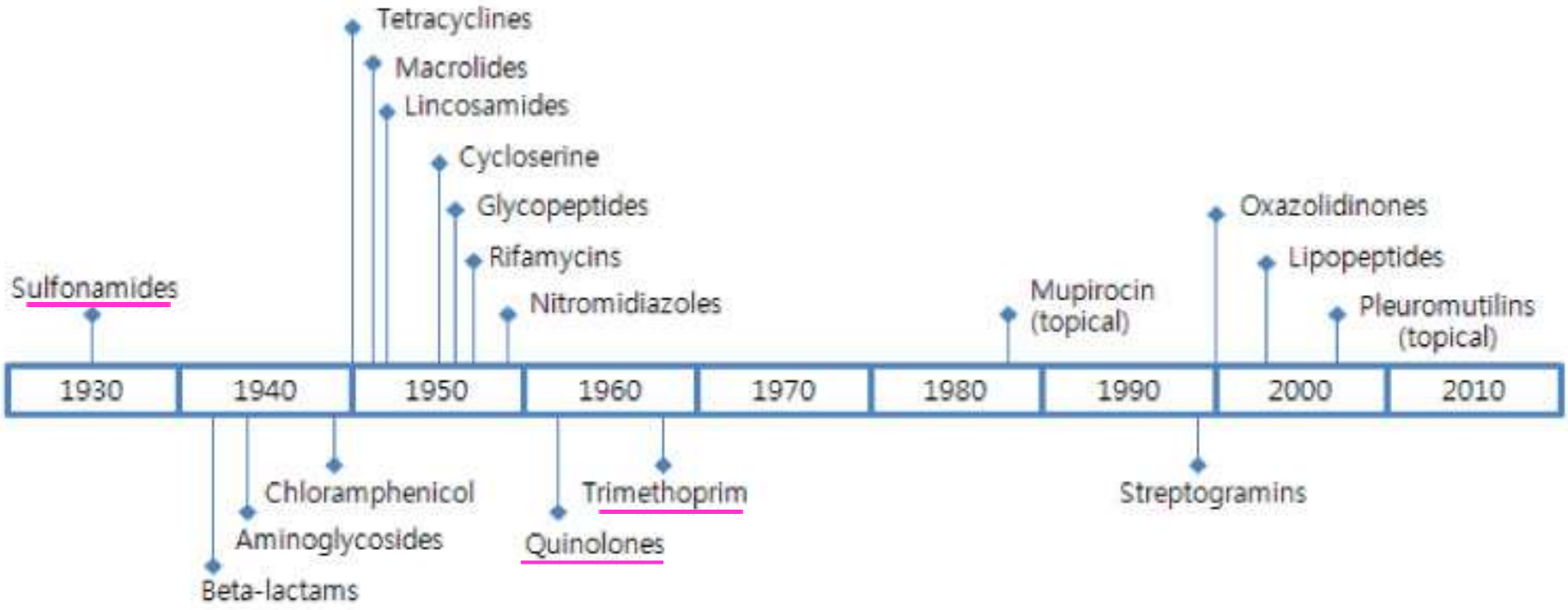
DNA gyrase inhibitors, antifolates and antimalarial drugs

2019

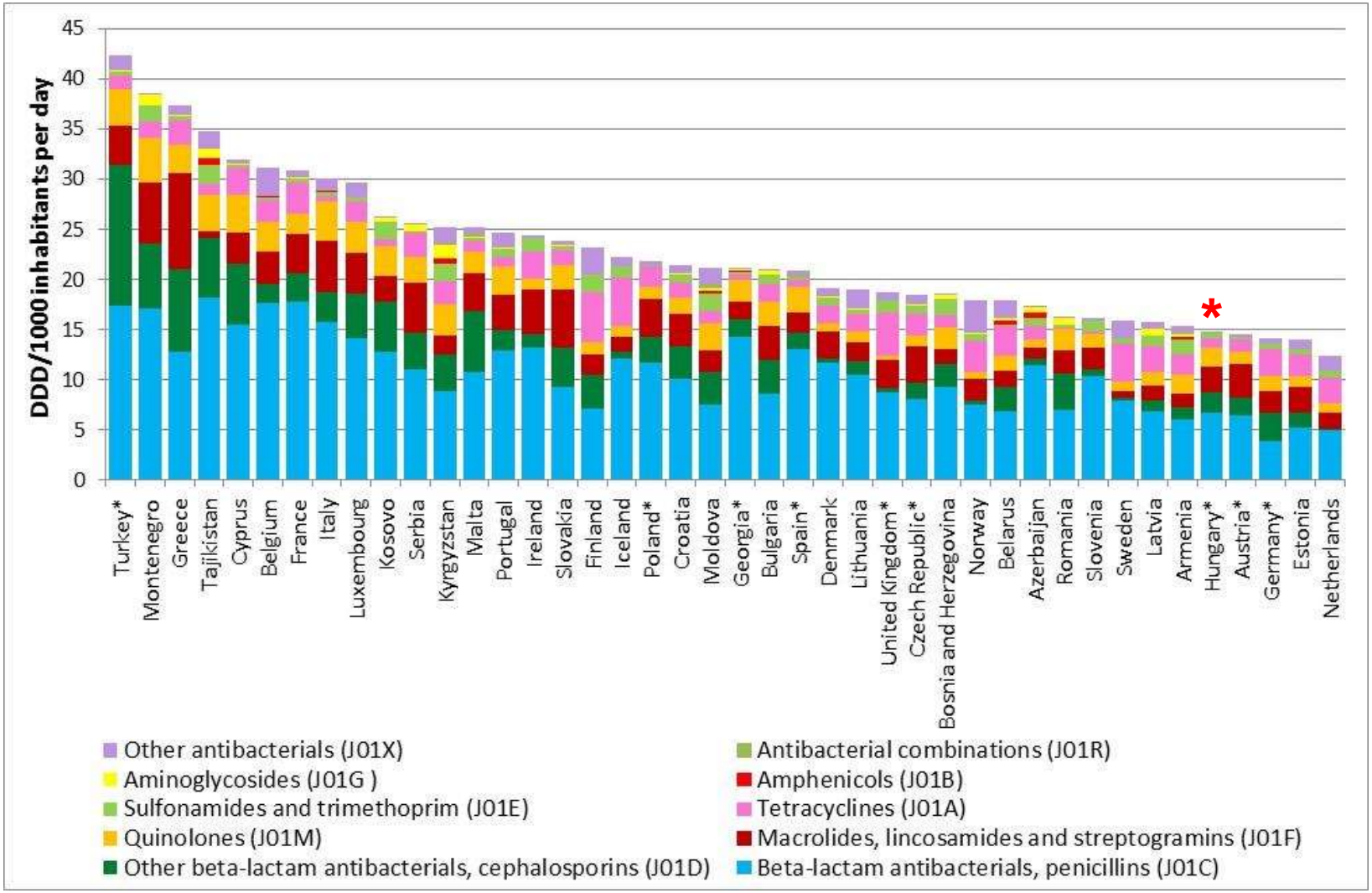
Mechanism of action of antimicrobial agents



History of antimicrobial drug development

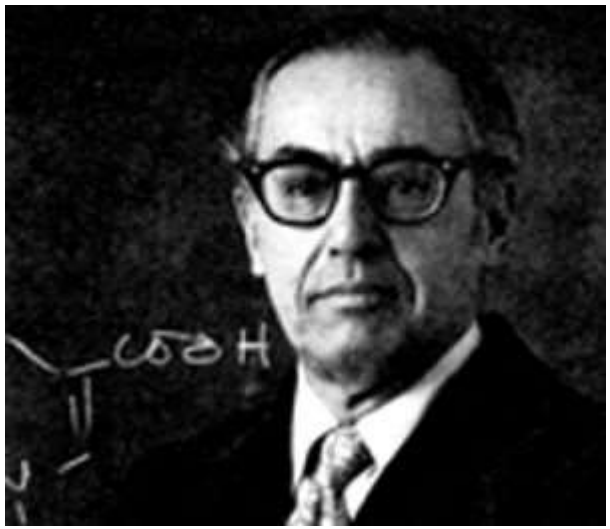


Data on antibiotic use

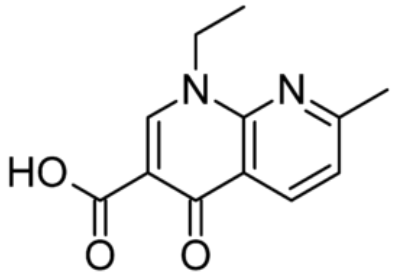


History of DNA gyrase inhibitors

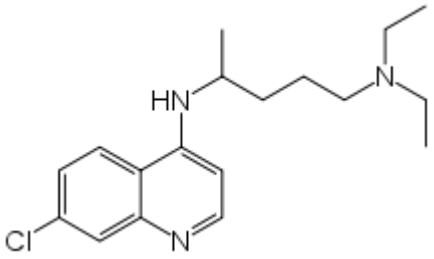
George Lesher



Nalidixic acid – 1962



Chloroquine



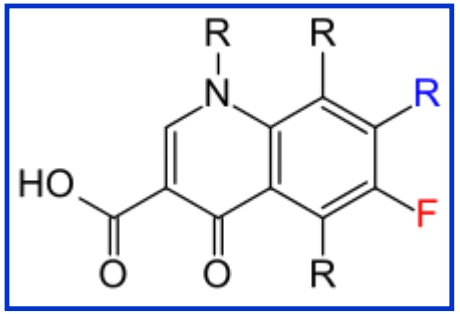
DNA gyrase inhibitors

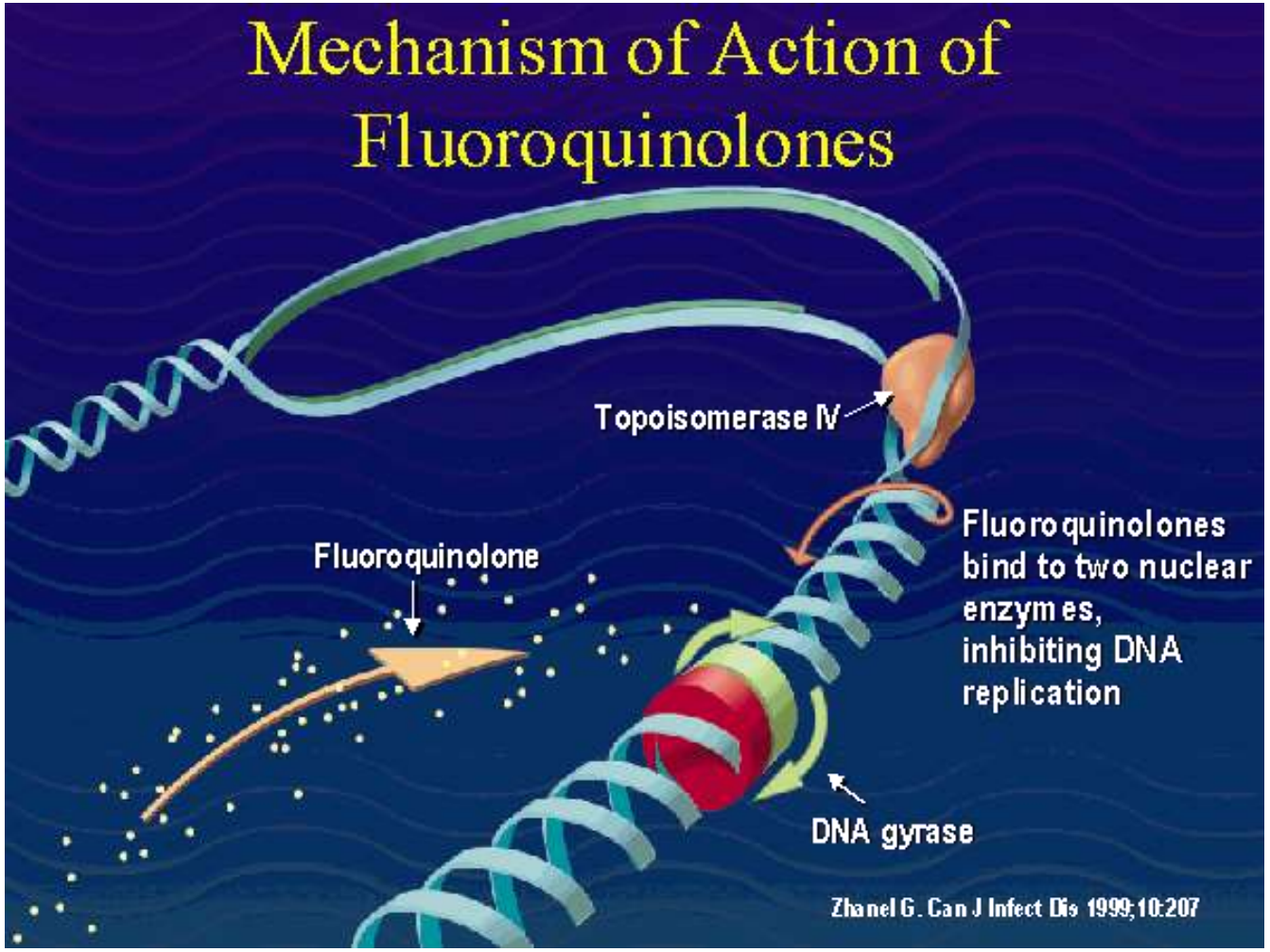
Quinolones – oldest, non fluorinated

- 0. generation: nalidixic acid, oxolinic acid
- Antimicrobial spectrum: Gram-negative bacteria (resistance)
- Pharmacokinetics: orally
- Indications: only used for urinary tract infections

Fluoroquinolones - 1980

nalidixic acid derivatives
adding fluorine to the quinolone ring
activity increase significantly





-They inhibit the replication of bacterial DNA by interfering with the action of
topoisomerase II (DNA gyrase) and
topoisomerase IV during bacterial growth and reproduction.

- Broad-spectrum antibiotics, with bactericidal activity.
- Post-antibiotic effect .

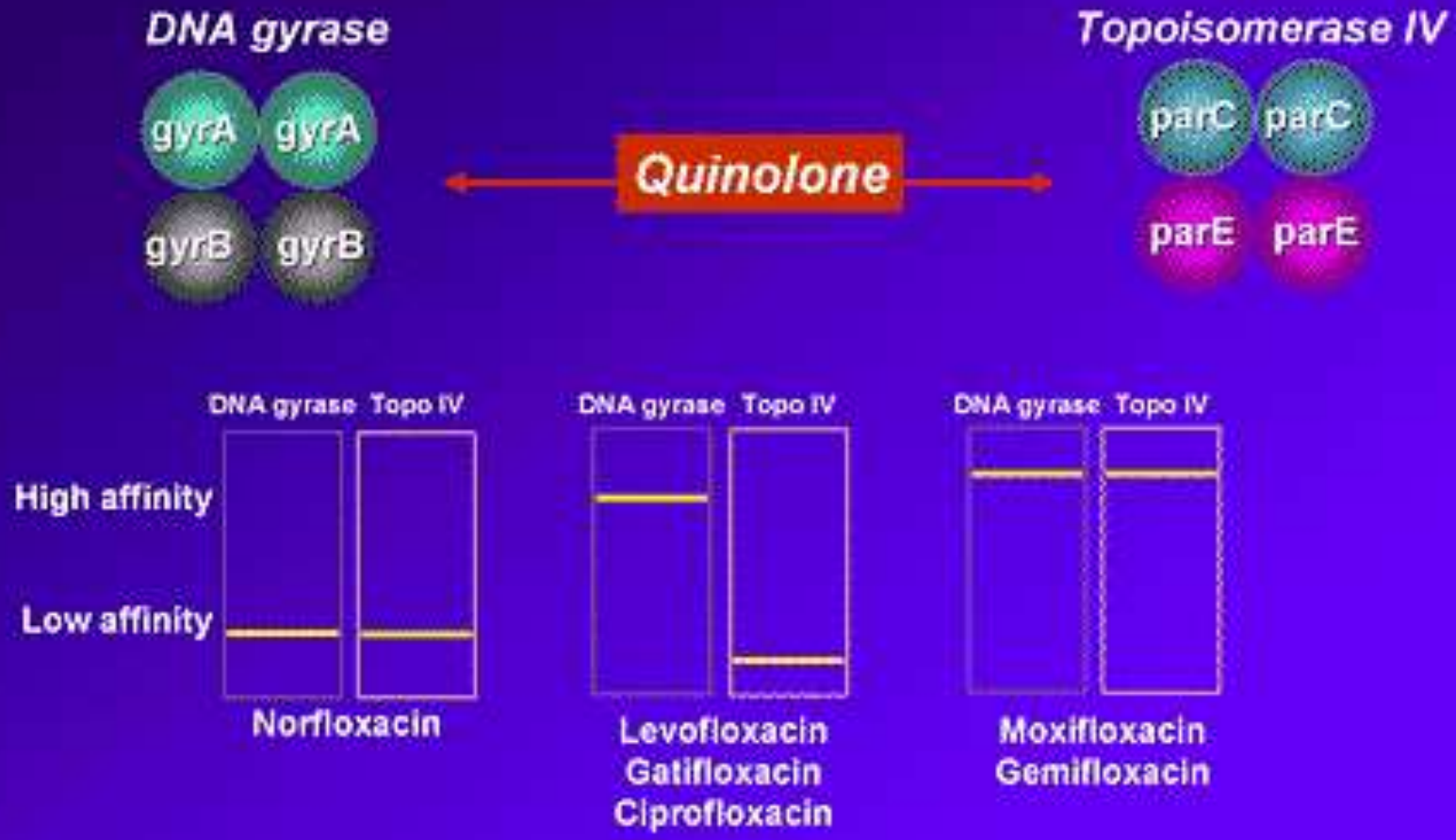
Classification of quinolones, fluoroquinolones

- *0. gen.: nalidixix acid, oxolinic acid*
- 1. gen.: norfloxacin
- 2. gen.: pefloxacin, ofloxacin, ciprofloxacin
- 3. gen.: levofloxacin, sparfloxacin
- 4. gen.: moxifloxacin, gemifloxacin

Withdrawn drugs: gatifloxacin (hypo- and hyperglycemia)
grepafloxacin (cardiac events)
trovafloxacin (hepatotoxicity)

New development
5. generation: delafloxacin, ozenoxacin

Quinolones and Bacterial DNA Targets



Antimicrobial spectrum of quinolones and fluoroquinolones

	Staph. cocc.	Strept. cocc.	Entero- cocc.	Anaerob B. frag.	G (-) E.coli…	Ps. aer.	Mycopl. Chlam.
0. Gen.					+		
1. Gen					++	+	
2. Gen	+	+			++	++	+
3. Gen	++	++			+++	++	++
4. Gen	++	+++		++	+++	++	+++

Clinical uses

- 0. gen: uncomplicated urinary tract infection
- 1. gen: urinary tract infection + gastroenteritis
- 2. gen: Gram (-) systemic infection (except meningitis)
  ciprofloxacin – most commonly used
  first line – B. antrasis attacks (for emergencies)
- 3. gen: Gram (+), Gram (-) systemic infection
  first line in nosocomial respiratory tract infection
- 4. gen: Gram (+), Gram (-), systemic infection
  mixed infection (aerob + anaerob) in monotherapy
  or in combination with aminoglycosides

Pharmacokinetics

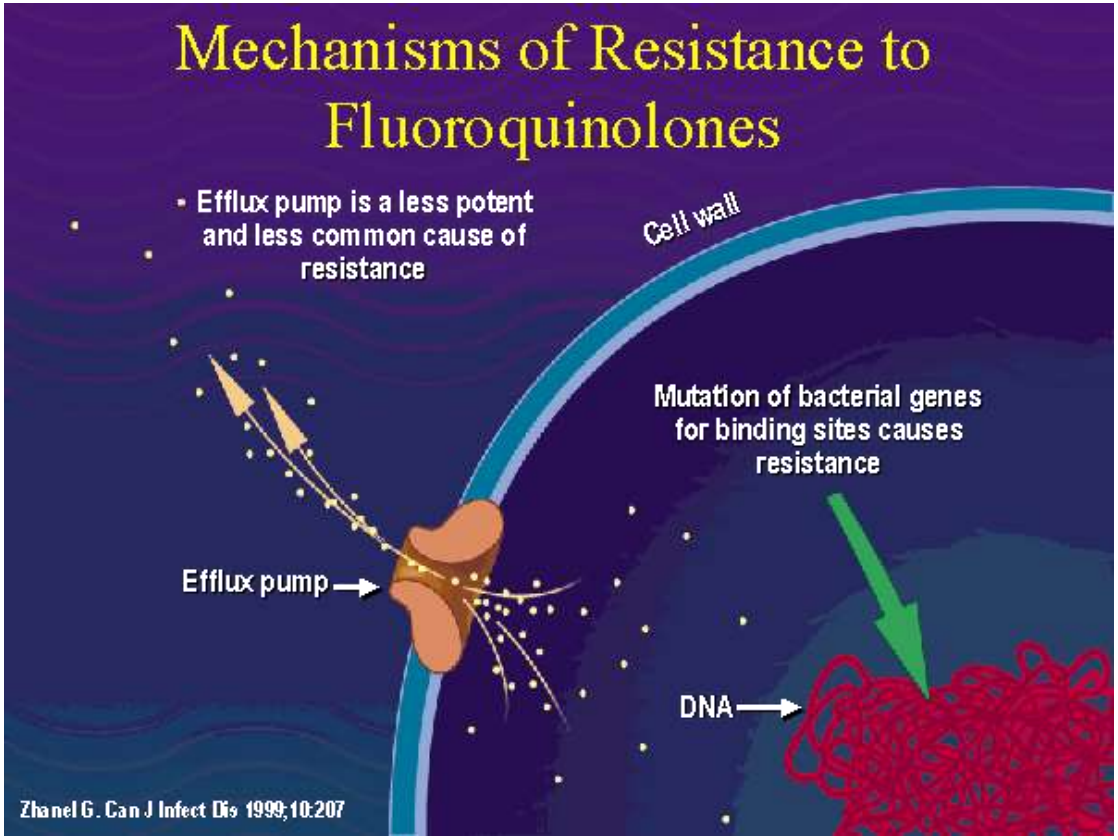
- Orally well absorbed (bioavailability 80-95%)
- Distributed widely in body fluids and tissue
- Relatively long half-life:

  3h – norfloxacin, ciprofloxacin
  10h – perfloxacin (once daily dose)
  20h – sparfloxacin

- Eliminated by renal mechanism
- Divalent and trivalent cations form chelates

Adverse effects

- GI
- CNS: headache and dizziness, mental disorders
- Photosensitivity (except ofloxacin)
- Liver toxicity: only trovafloxacin is associated with serious liver injury (max. 14 days)
- QT interval prolongation (arrhythmias) may occur (3., 4 gen)
- Articular cartilage damage, Achilles-tendon rupture
- Hypo- and hyperglycemia among diabetic patients (moxifloxacin)
- Contraindicated in pregnancy and in children under 18 years of age



Mutation in the bacterial DNA gyrase and topoisomerase IV associated with a decreased affinity for fluoroquinolones.

Decreased accumulation –

- decreased number of porin protein in the outer membrane and
- increased efflux pump activity

Cross-resistance exists among the quinolones

There is no cross-resistance between beta-lactams and aminogylcosides

Problems with development of bacterial resistence to fluoroquinolones

- Staphylococci (MRSA) 60-95%
- Pseudomonas aeruginosa 5-30%
- Escherichia coli 8-26%
- Neisseria gonorrheae 6-70%
- Streptococcus pneumoniae 3%

Drug interactions

Drugs **increasing** levels of fluoroquinolones

- Theophylline
- NSAIDs
- Corticosteroids

Fluoroquinolones increasing the level of:

- Warfarin (INR – monitored)
- Antidepressants
- Imipramine
- Caffeine
- Theophylline

Sulfonamides, trimethoprim

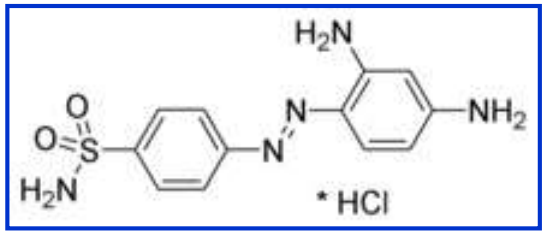
Domagk 1932,

GERHARD DOMAGK
1895-
The investigator who discovered the anti-infective action of the sulfonamide drugs

"Prontosil enables the mouse infected with streptococci to live if it is treated subcutaneously or orally with the drug within 24 hours of the beginning of the infection."

Prontosil – wool dye

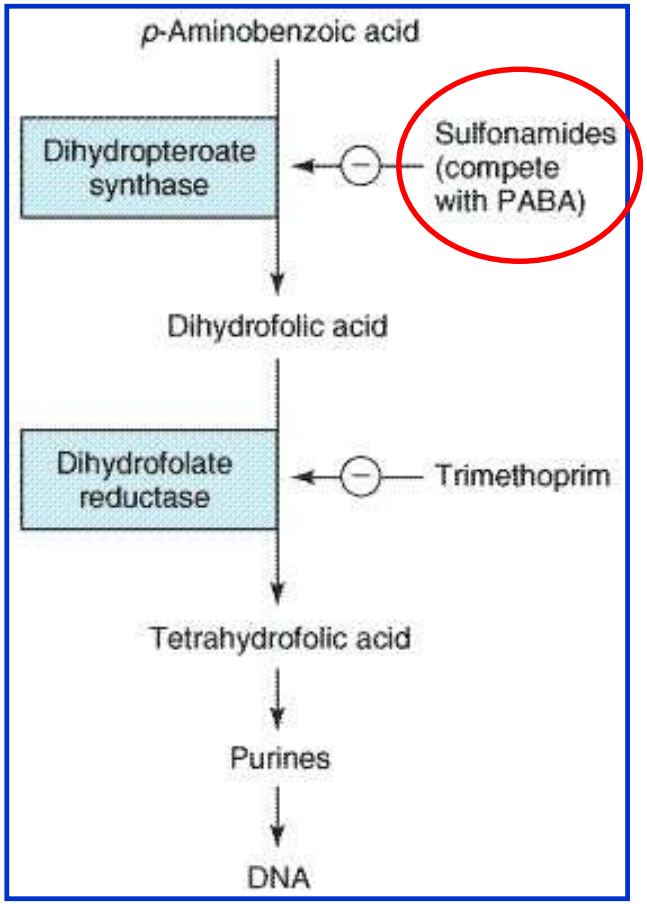
prodrug



Metabolite:
p-amino-sulfo-benzoic acid

Mechanism of action of sulfonamides

- Many bacteria are impermeable to folic acid
- They synthesize folate de novo
- Folic acid is synthesized from PABA
- All sulfonamides are PABA analogues
- Sufonamides inhibit the dihydropteroate synthetase



Antibacterial spectrum of sulfonamides

- Streptococcus pyogenes
- Neisseria meningitidis
- E. coli
- Chlamydia
- Toxoplasma
- Nocardia
- Chloroquine-resistant malaria

Pharmacokinetics of sulfonamides

- orally well absorbed (except: sulfasalazin-ulcerative colitis and enteritis)
- Sulfa drugs acetylated primarily in the liver
- Crystalluria - „stone formation” at neutral or acidic pH

Adverse effects of sulfonamides

- Hypersensitivity, allergy (5-8%)
- nephrotoxicity
- In newborns may occur Kern-icterus

  (sulfa drugs displace bilirubin from binding sites on serum albumin,
  the bilirubin is then free to pass into the CNS,
  because the baby’s BBB in not developed)
- Contraindication in newborns and in pregnancy

Clinical uses of sulfonamides

only in combination with trimethoprim

- To use of combination is based on the in vitro synergy of the two compound
- Bactericidal antibiotic effect

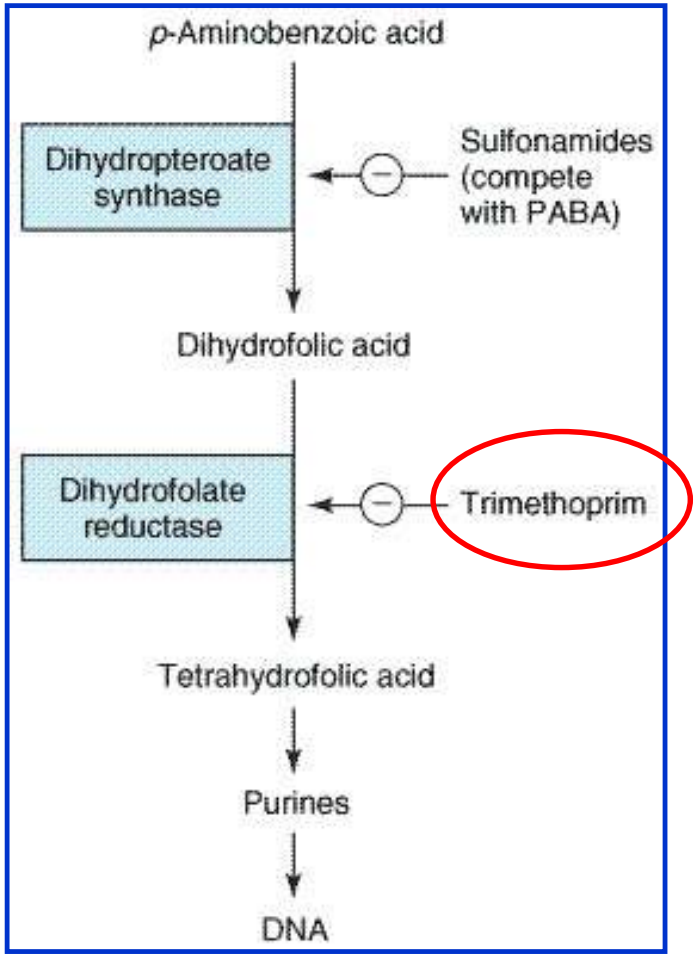
Trimethoprim

discovered during the research of the anti-malariac drugs

Mechanism of action of trimethoprim

inhibit the dihydrofolate reductase

The combination of trimethoprim with sulfamethoxazole called co-trimoxazole



Antibacterial spectrum of the combination

Co-trimoxazole has a broader spectrum than sulfa drugs.

It is effective in Pneumocystis carinii and jiroveci pneumonia and ampicillin- and chloramphenicol-resistant systemic salmonella infections

Resistance

to the combination may occur as a result of mutations that cause

(1) Overproduction of PABA
(2) Overproduction of enzymes

Pharmacokinetics of the combination

- Similarity in the half-lifes of the two drugs
- Orally well absorbed
- Both parent drugs and their metabolites are excreted in the urine

Adverse effects of combination

- GI
- megaloblastic anemia, leukopenia, thrombocytopenia
- allergy (sulfa component), skin rash
- nephrotoxicity (because of the sulfa component, crystalluria)
- Contraindicated in pregnancy

Clinical uses of the combination

- Urinary tract infections
- Respiratory tract infections
  (H. influenzae, Legionella, Pneumocystis carinii, jiroveci)
- Prophylaxis is recommended for HIV-infected patients
- GI-infections (shigellosis, salmonella typhi)
- In sepsis and meningitis caused by Listeria

Antimalarial drugs

2019

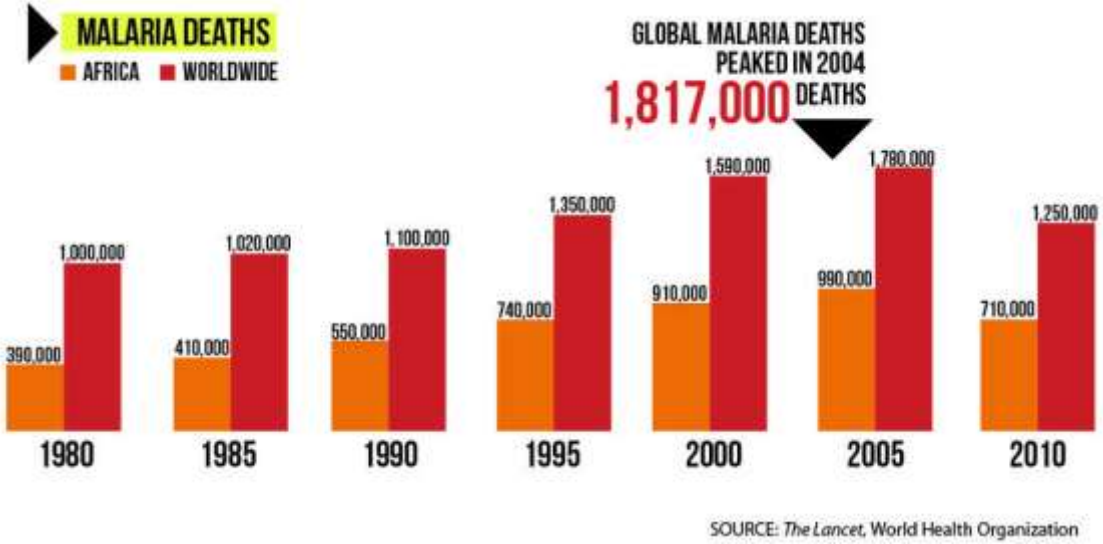
60 SECONDS TO CHANGE

MALARIA BY THE NUMBERS

A CHILD DIES FROM MALARIA EVERY **60** SECONDS

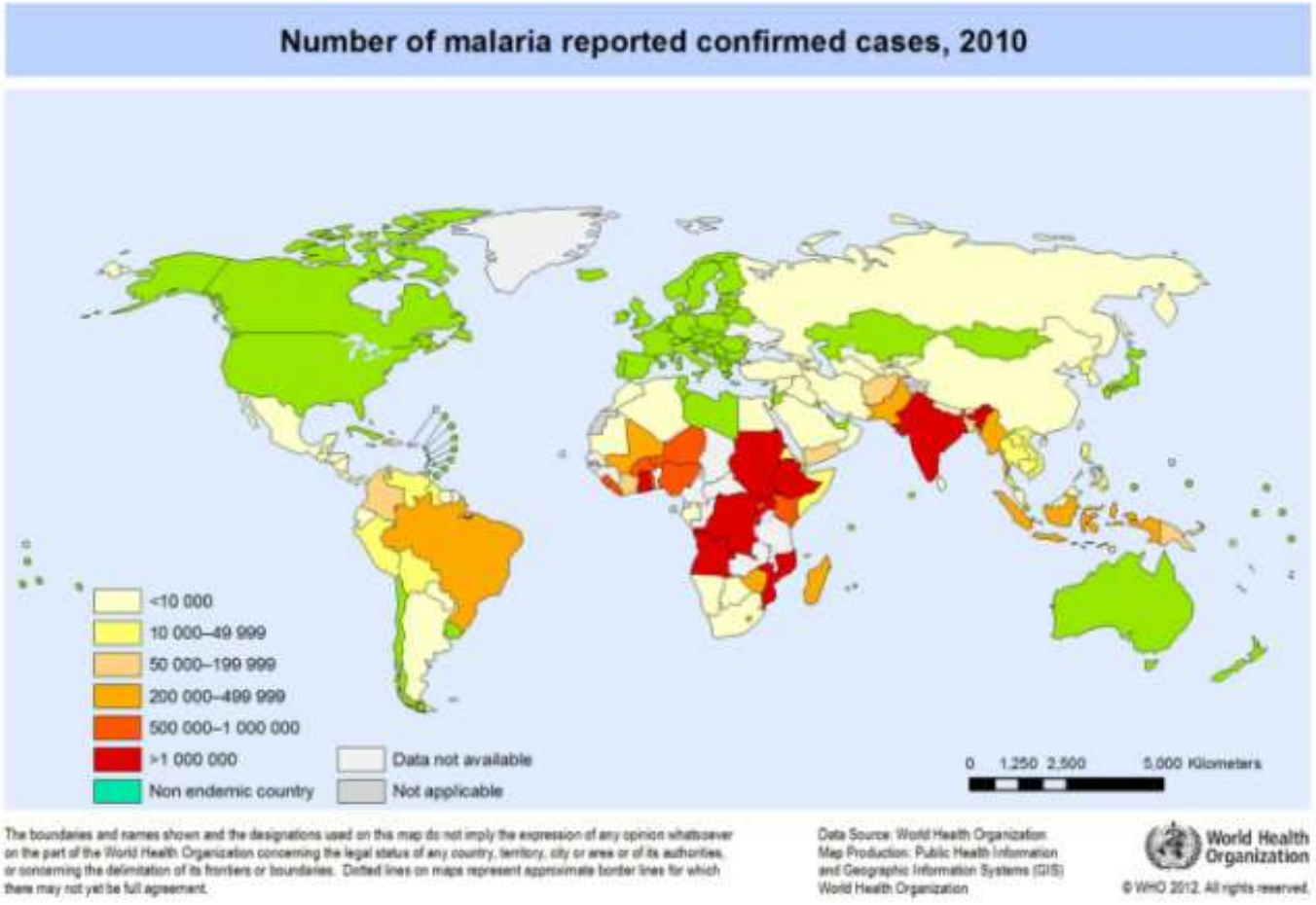
IN 2010, **219** MILLION PEOPLE WERE DIGANOSED WITH MALARIA

90 % OF ALL MALARIA CASES OCCUR IN AFRICA



SOURCE: *The Lancet*, World Health Organization

GLOBAL PREVALENCE OF MALARIA



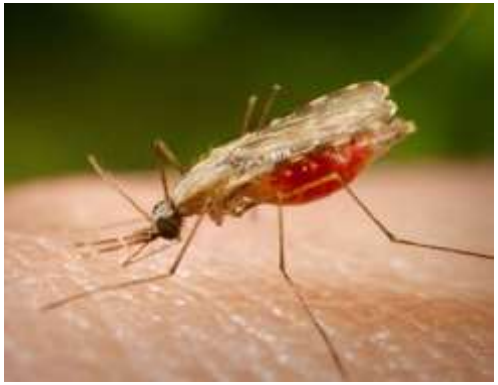
- More than 100 countries are endemic (WHO)
- It is not only tropical disease today

MALARIA

Alphonse Laveran (1845-1922)

Malaria is a life-threatening disease caused by parasites. It is preventable and curable.

Transmitted by the female Anopheles mosquitoes.

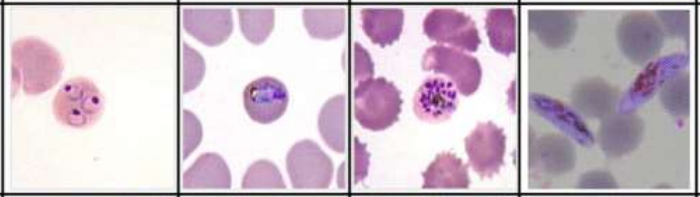
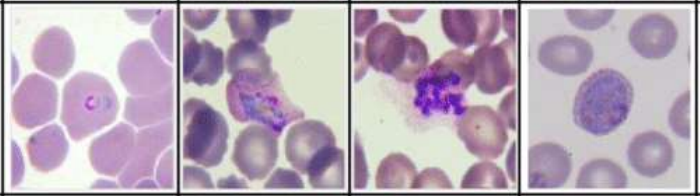
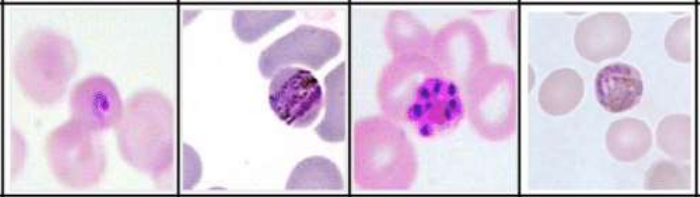
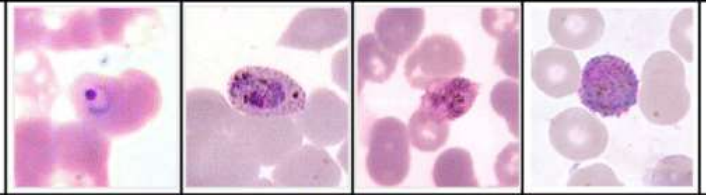
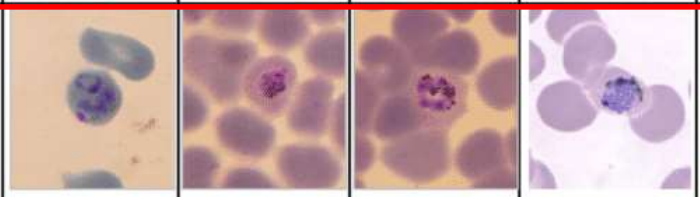


Human Plasmodium species

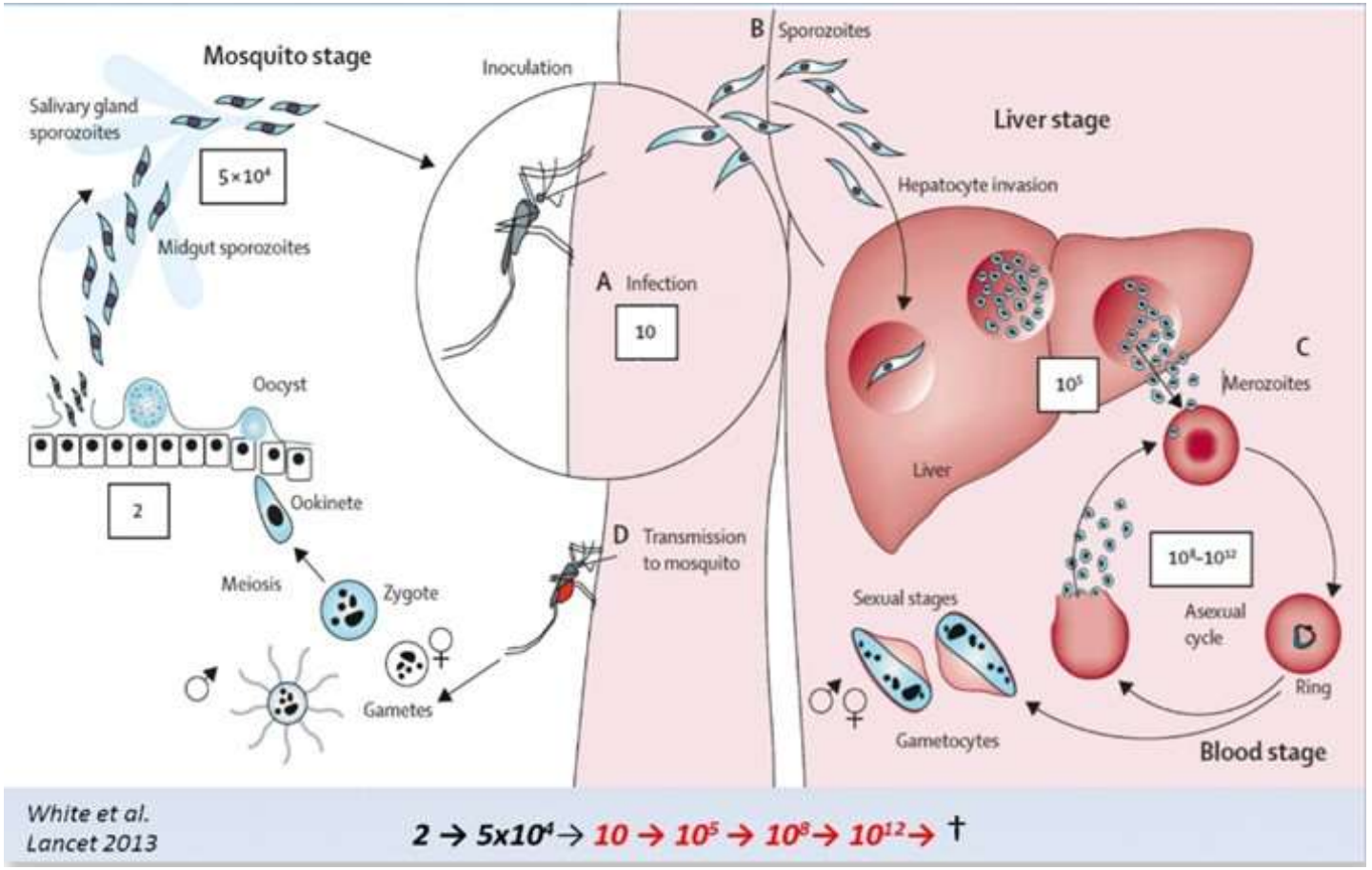
P. – Plasmodium

P. vivax – occurs in Mediterranean countries such as Italy, Greece, Spain and Corsica

Human Malaria

Species \ Stages	Ring	Trophozoite	Schizont	Gametocyte	
P. falciparum					• *Parasitised red cells (pRBCs) not enlarged.* • *RBCs containing mature trophozoites sequestered in deep vessels.* • *Total parasite biomass = circulating parasites + sequestered parasites.*
P. vivax					• *Parasites prefer young red cells* • *pRBCs enlarged.* • *Trophozoites are amoeboid in shape.* • *All stages present in peripheral blood.*
P. malariae					• *Parasites prefer old red cells.* • *pRBCs not enlarged.* • *Trophozoites tend to have a band shape.* • *All stages present in peripheral blood*
P. ovale					• *pRBCs slightly enlarged and have an oval shape, with tufted ends.* • *All stages present in peripheral blood.*
P. knowlesi					• *pRBCs not enlarged.* • *Trophozoites, pigment spreads inside cytoplasm, like P. malariae, band form may be seen* • *Multiple invasion & high parasitaemia can be seen like P. falciparum* • *All stages present in peripheral blood.*

LIFE CYCLES OF MALARIA



A./ Inside the mosquito the parasite differentiates into a new form **(sporozoites)** and enters the salivary glands.
B./ It is injected into the human host when the mosquito feeds. Within minutes the parasite will reach the human liver cells when the parasite will differentiate into a new form **(merozoit)**. It will multiply inside the liver cells.
C./ After the asexual cycle **gametocytes** will develop.
D./ The parasite is taken into the female mosquito stomach when it feeds from someone infected with malaria.

Symptoms of malaria

Incubation: P. falciparum 9-14 days

P. vivax, P. ovale - months

P. malariae – years (40 years !!)

General symptoms:

chills, fever, headache, sweating, back and joint pain

anemia, hemolysis, respiratory distress, consciousness,

kidney and liver failure

Fever: irregular high fever – P. falciparum

every 24 hours – P. knowlesi

every 48 hours – P. vivax, P. ovale

every 72 hours – P. malariae

GI symptoms: nausea, vomiting, diarrhea

Classification of drugs used for treatment of malaria

tissue schizonticides	act on liver forms e.g. PRIMAQUINE
blood schizonticides (suppressive therapy)	act on erythrocyte forms, prevent the clinical symptoms e.g. CHLOROQUINE, QUININE
gametocides	kill gametocytes e.g. PRIMAQUINE
sporontocides	act in the mosquitoes, prevent the transmission of parasites, e.g.. PRYMETHAMINE
secondary tissue schizonticides (radical therapy)	act on the secondary (exoerythrocytic) liver forms e.g. PRIMAQUINE against Pl. vivax or ovale
prophylactic therapy	

Treatment of malaria

4-aminoquinolines

Chloroquine

Mechanism of action: **blood schizonticide**
concentrates in parasites, inhibit DNA transcription and replication

Pharmacokinetics: **good oral absorption,**
accumulation in the tissues, half-life ~ 5 days

Adverse effects: **well tolerated if not high doses are given**

Contraindications: **psoriasis,**

Clinical uses: **suppressive therapy, prophylaxis**
amebic liver abscess (with metronidazole)

Treatment of malaria

quinoline methanols

Quinine and quinidine (cinchona tree alkaloid)

Mechanism of action: blood schizonticide,
gametocide against P. vivax and ovale

Pharmacokinetics: good oral absorption, (or iv.!, not im.)

Adverse effects:
cinchomism – vomiting, flushing, visual and auditory disturbances, abdominal pain
in overdosage - cardial effects !!!

Contraindications: cinchonism, hypersensitivity

Clinical uses: parenteral in severe falciparum malaria
oral - suppressive therapy

Treatment of malaria

quinoline methanols

Mefloquine

Mechanism of action: blood schisonticide and gametocide against P. vivax and ovale

Pharmacokinetics: good oral absorption, used only orally

Adverse effects: GI, central symptoms

Contraindications: psychiatric disorders, epilepsy, not together with quinine

Clinical uses: suppressive therapy first of all in case of resistance
prophylaxis in case of known resistance

Treatment of malaria

8-aminoquinolines

Primaquine

Mechanism of action: tissue schizonticide (also gametocide)

Pharmacokinetics: good oral absorption, used only orally

Adverse effects: well tolerated; with higher dose GI, rarely leucopenia, methaemoglobinaemia, hypersensitivity

Clinical uses: radical therapy against P. vivax and ovale
pneumocystis carinii (in combination with clindamycin)

Treatment of malaria

inhibitors of folate synthesis

Proguanil, Pyrimethamine,

Clinical uses:

pyrimethamin + sulfadoxin

for chemoprophylaxis in case of chloroquine-resistant P falciparum

Treatment of malaria

Others

artemisinin (natural) and its derivatives

Antimalarial action: **blood schizonticide (rapid action)**

Pharmacokinetics: **good absorption (p.o.; i.v.; i.m.; rectal)**
active metabolite - dihydroartemisin

Antibiotics

tetracyclines, clindamycin

Clinical uses: **multiresistant P falciparum**

Treatment of malaria

Uncomplicated malaria

symptomatic malaria without signs of severity or evidence of vital organ dysfunction
parazitaemia <5%

chloroquin,
artemisin deriv. + mephloquine or lumefantrine or atovaquone or quinine in combination doxycycline or clindamycin

Compliced malaria

vital organ dysfunction
acut, severe form when parazitaemia is > 5%

1st day: artemisin or kinin + docycyclin or clindamycin parenterally
from 2nd day: per os treatment

Treatment of malaria in pregnancy

Uncomplicated malaria

1. trimester: quinine or clindamycine
2-3. trimester: arthemeter + lumefantrine

alternative: artesunat + clindamycin or quinine+clindamycin

Complicated malaria

1. trimester: artesunat or quinine
2-3. trimester: artesunat