Advances in the treatment of Infectious diseases with special focus on advancements in antimalarial drug delivery systems

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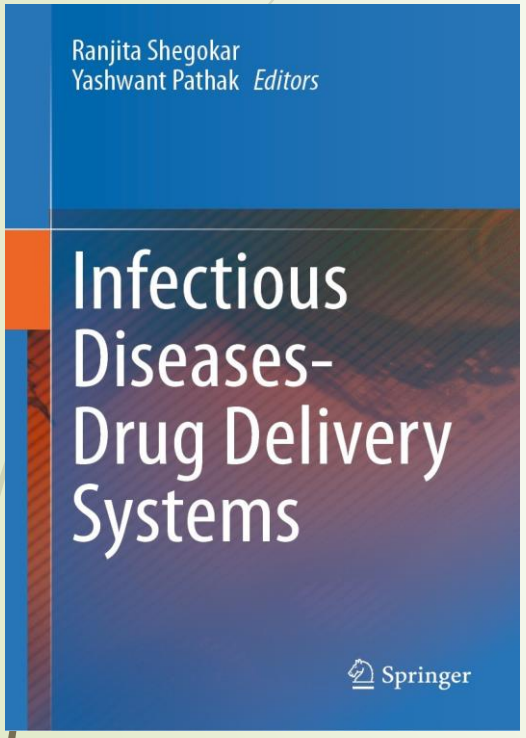
Dobré odpoledne

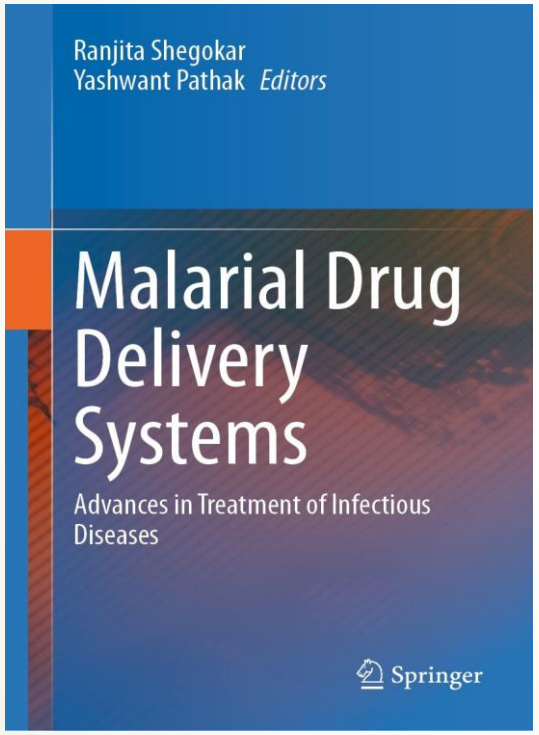
- Jak se všichni máte (How are you all)
- Omlouvám se, omlouvám se (My apologies)
- Neumím mluvit česky (I cannot speak Czechia Language)
- Doufám, že rozumíte mé angličtině a že se můžete kdykoliv během přednášky na něco zeptat (hope you will understand my english, you can ask me questions anytime during the lecture)
- Díky Google překladači (Thanks to Google translator)

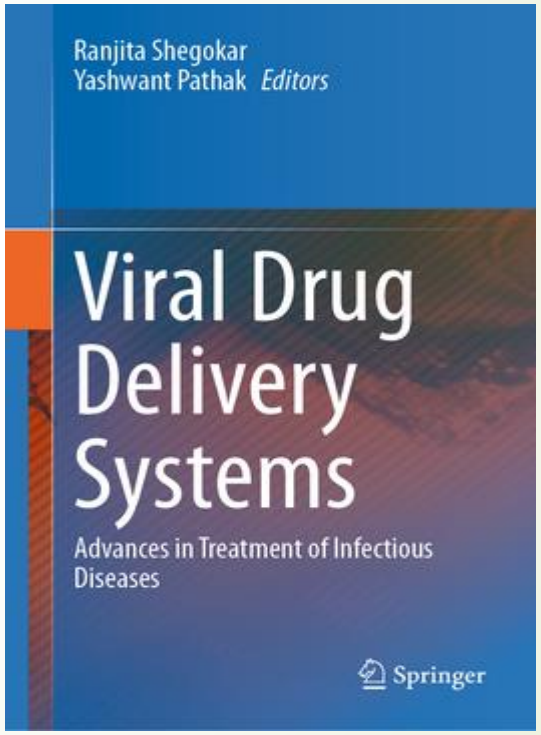
Brno miluji

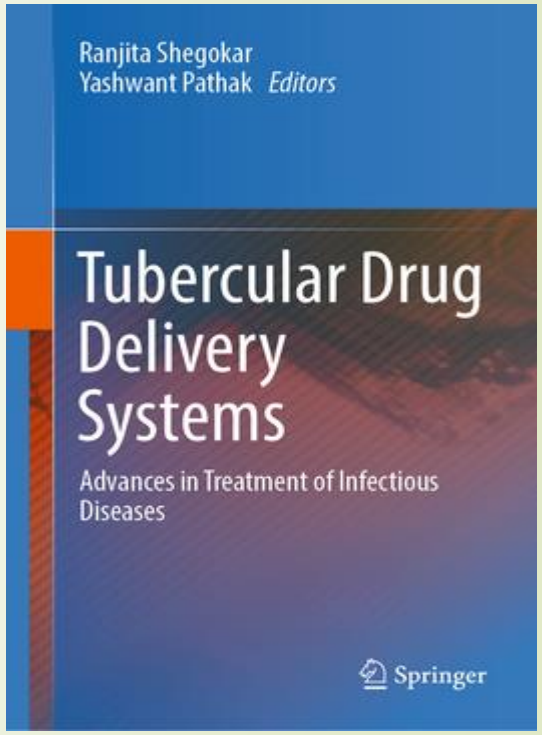
- Beautiful City
- Wonderful People
- Efficient Transportation
- Great Food
- Excellent Faculty of Pharmacy facilities and faculty Personnel

Our recent books published on Infectious diseases









Publisher Springer Nature, Published in 2023

Key facts: Malaria

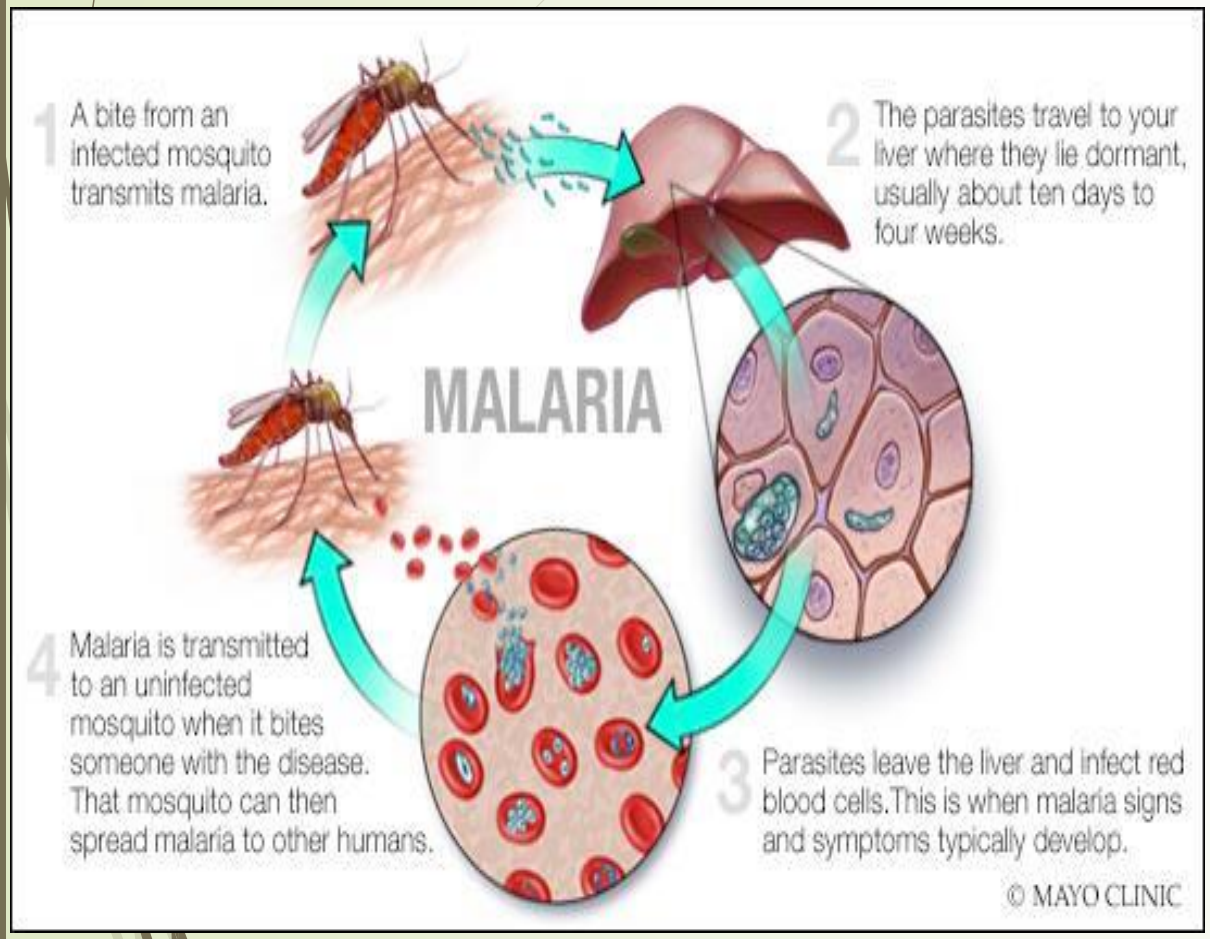


Figure taken from https://www.mayoclinic.org/diseases-conditions/malaria/symptoms-causes/syc-20351184

- In 2021, nearly half of the world's population was at risk of malaria.
- That year, there were an estimated 247 million cases of malaria worldwide.
- The estimated number of malaria deaths stood at 619 000 in 2021.
- The WHO African Region carries a disproportionately high share of the global malaria burden. In 2021, the Region was home to 95% of malaria cases and 96% of malaria deaths. Children under 5 accounted for about 80% of all malaria deaths in the Region.

Overview on Malaria

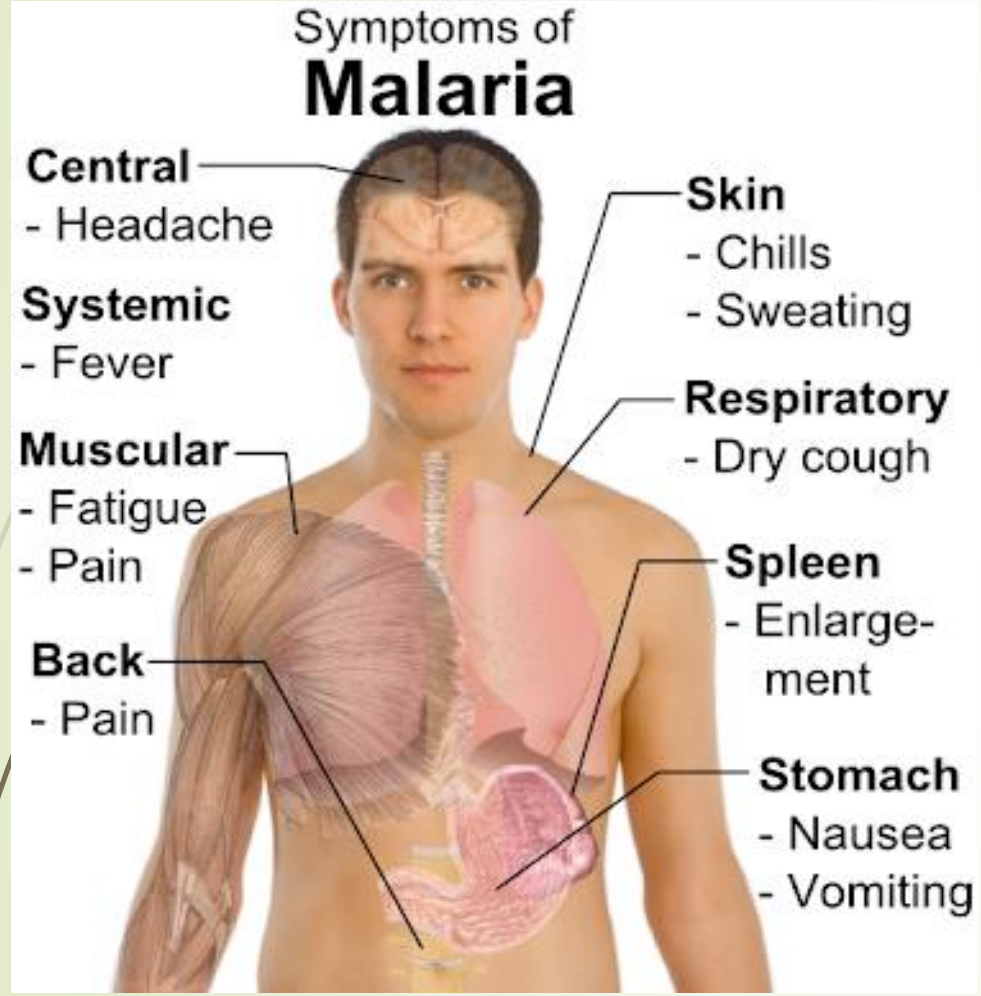


Figure taken from https://sites.google.com/a/cornell.edu/public-health-care-sustainability-malaria-in-sub-sahara-africa/introduction

- Malaria is a disease caused by a parasite. The parasite is spread to humans through the bites of infected mosquitoes. People who have malaria usually feel very sick with a high fever and shaking chills.
- While the disease is uncommon in temperate climates, malaria is still common in tropical and subtropical countries. Each year nearly 290 million people are infected with malaria, and more than 400,000 people die of the disease.

Taken from https://www.mayoclinic.org/diseases-conditions/malaria/symptoms-causes/syc-20351184

Overview on Malaria

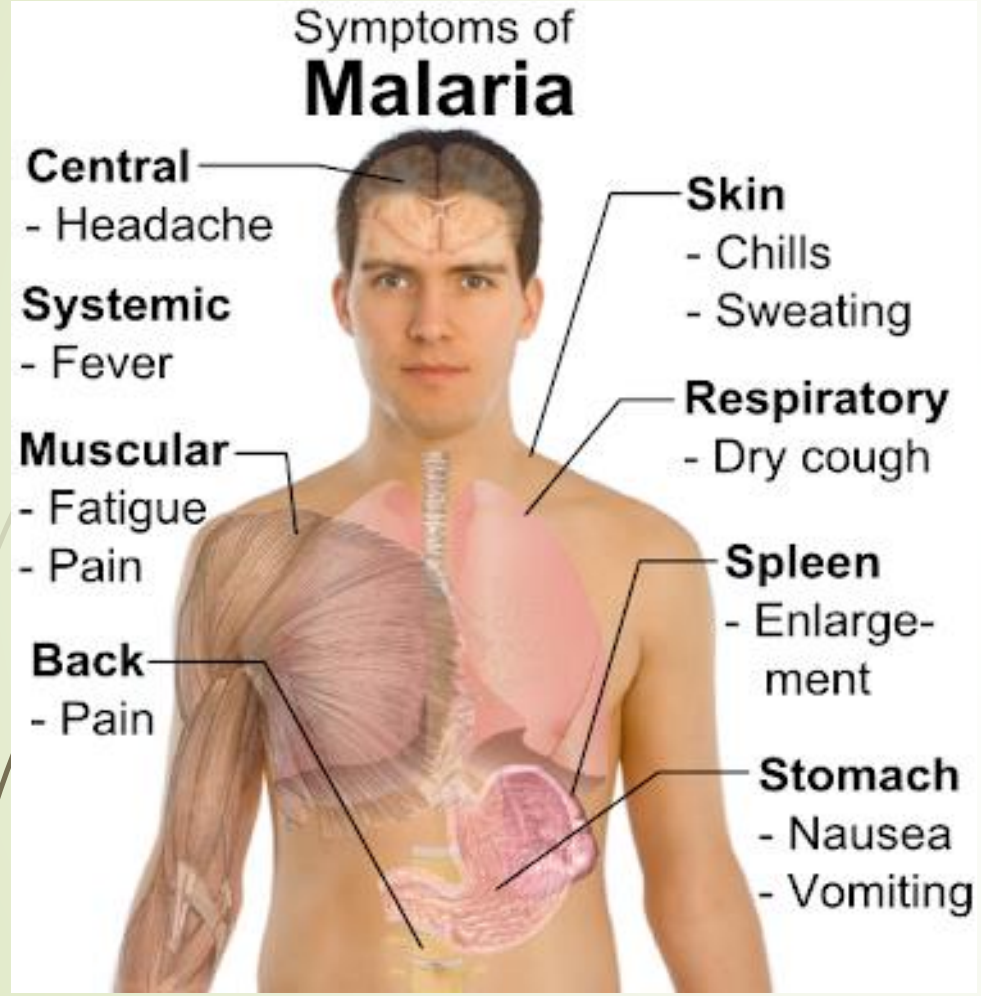
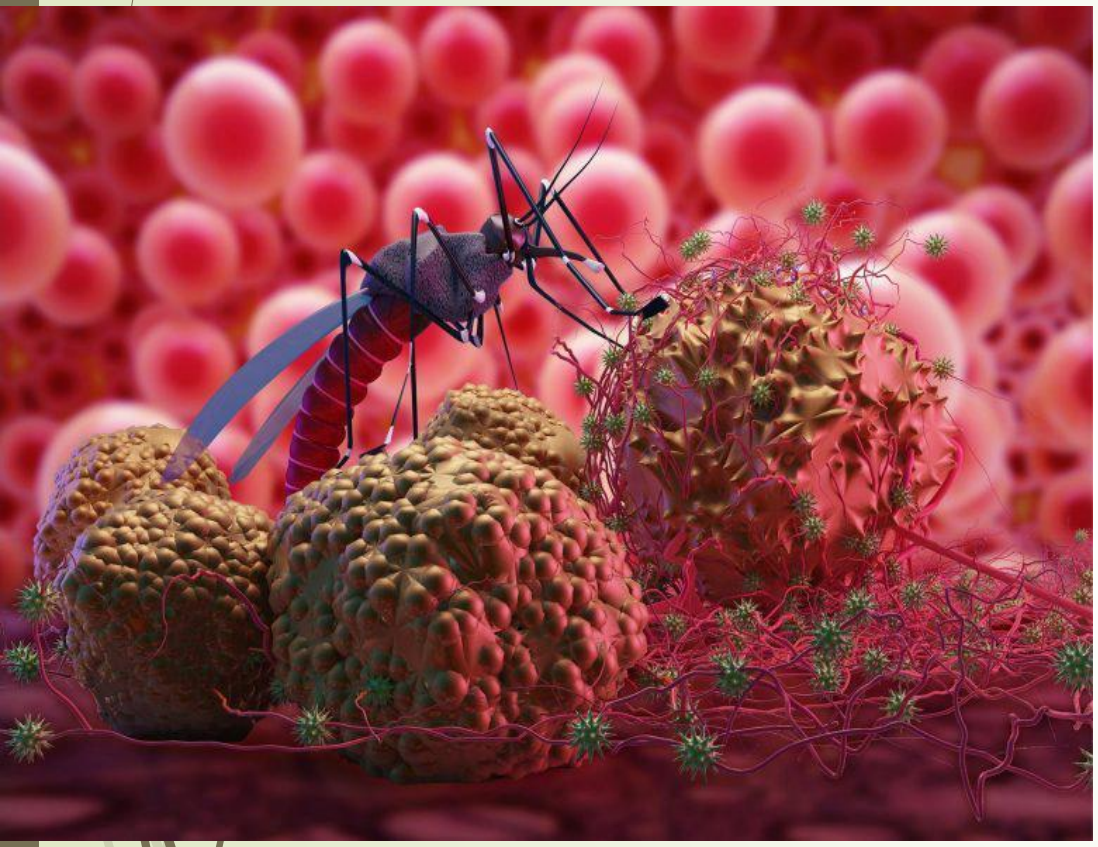


Figure taken from https://sites.google.com/a/cornell.edu/public-health-care-sustainability-malaria-in-sub-sahara-africa/introduction

- To reduce malaria infections, world health programs distribute preventive drugs and insecticide-treated bed nets to protect people from mosquito bites. The World Health Organization has recommended a malaria vaccine for use in children who live in countries with high numbers of malaria cases.
- Protective clothing, bed nets and insecticides can protect you while traveling. You also can take preventive medicine before, during and after a trip to a high-risk area. Many malaria parasites have developed resistance to common drugs used to treat the disease.

Taken from https://www.mayoclinic.org/diseases-conditions/malaria/symptoms-causes/syc-20351184

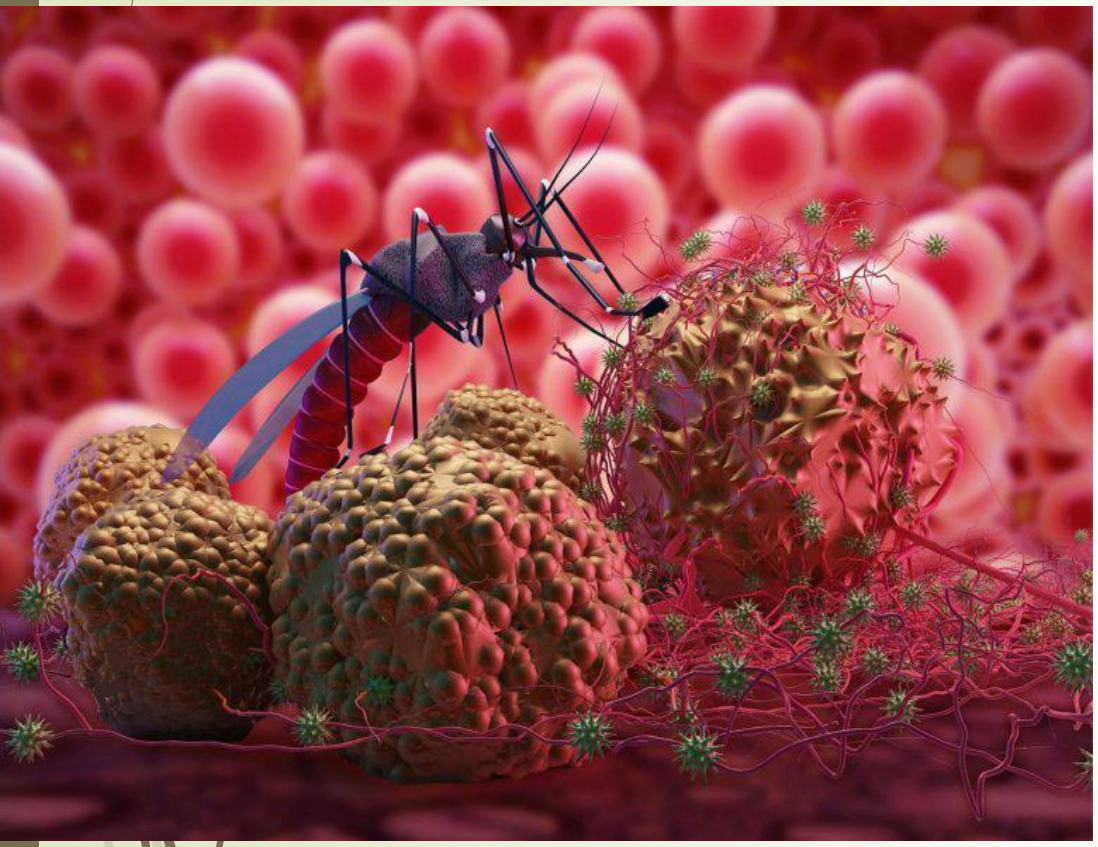
Factors that Influence Transmission



Malaria is a serious and sometimes fatal disease caused by a parasite that is transmitted to people through the bites of infected mosquitoes. Symptoms of malaria can range from mild to severe and include fever, chills, headache, muscle pain, and fatigue. In severe cases, it can cause anemia, low blood pressure, and organ failure.

- There are several factors that can influence the intensity of malaria transmission - factors that concern the human host, the mosquito vectors, the parasite itself, and the environment.
- Human immunity to malaria increases with age in populations that are at high risk for malaria infection. Many adults earn partial immunity after being exposed to the parasite for years, which does not offer complete protection from the disease but does provide some immunity. This is why malaria predominately affects young children in high-risk areas (however, in low-risk areas where little to now immunity is formed, all groups are at equal risk).

Factors that Influence Transmission



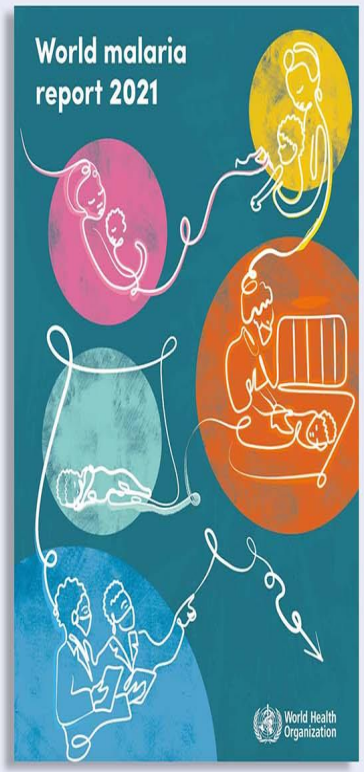
Malaria is a serious and sometimes fatal disease caused by a parasite that is transmitted to people through the bites of infected mosquitoes. Symptoms of malaria can range from mild to severe and include fever, chills, headache, muscle pain, and fatigue. In severe cases, it can cause anemia, low blood pressure, and organ failure.

- Anopheles mosquitos that transmit the Plasmodium parasite breed in water, but the different species all have unique and specific preferences that will allow them to breed more rapidly and efficiently. For example, some prefer shallow collections of water (like puddles, shallow ponds, or rice fields). The transmission is most intense in areas where the mosquito species' lifespan is longest, so that the parasite has time to become completely developed in the mosquito.
- Finally, the environment plays a large role in determining the intensity of transmission. In many areas of the world, malaria transmission is seasonal - highest during and just after the rainy season, when rainfall is heavy, temperatures are high, and the air is humid ('Malaria').

Professor Gerry Killeen in Lancet

- In the renowned journal *The Lancet*, Professor Gerry Killeen, the AXA Research Chair in Pathogen Ecology at University College Cork (UCC), states that the results of a major trial on bed nets treated with a combination of two insecticides instead of one highlight the significant impact that such combinations can have on reducing the burden of malaria in rural Africa.
- According to Professor Killeen, the trial clearly demonstrates the potential of these combinations to make a difference in the fight against the disease.

Global efforts to control malaria

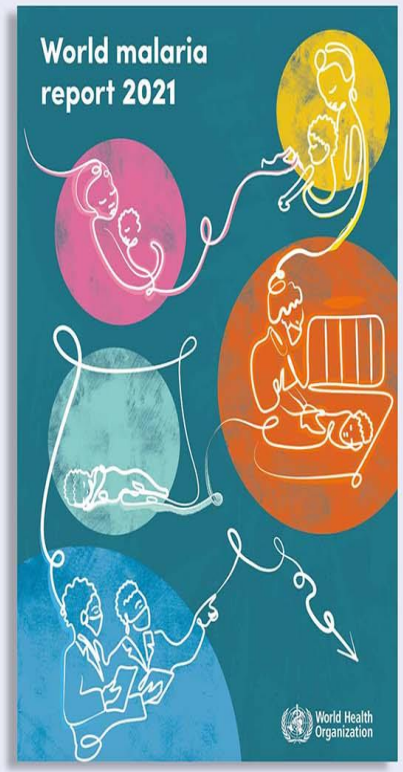


"To reach global targets, African governments must harness innovation and this will require rapid expansion of new, innovative and impactful tools."

WHO report

- In the past 150 years, roughly half of the countries in the world eliminated malaria. Nowadays, there are 99 endemic countries—67 are controlling malaria and 32 are pursuing an elimination strategy.
- This four-part Series presents evidence about the technical, operational, and financial dimensions of malaria elimination. The first paper in this Series reviews definitions of elimination and the state that precedes it: controlled low-endemic malaria.
- Feasibility assessments are described as a crucial step for a country transitioning from controlled low-endemic malaria to elimination.

Global efforts to control malaria

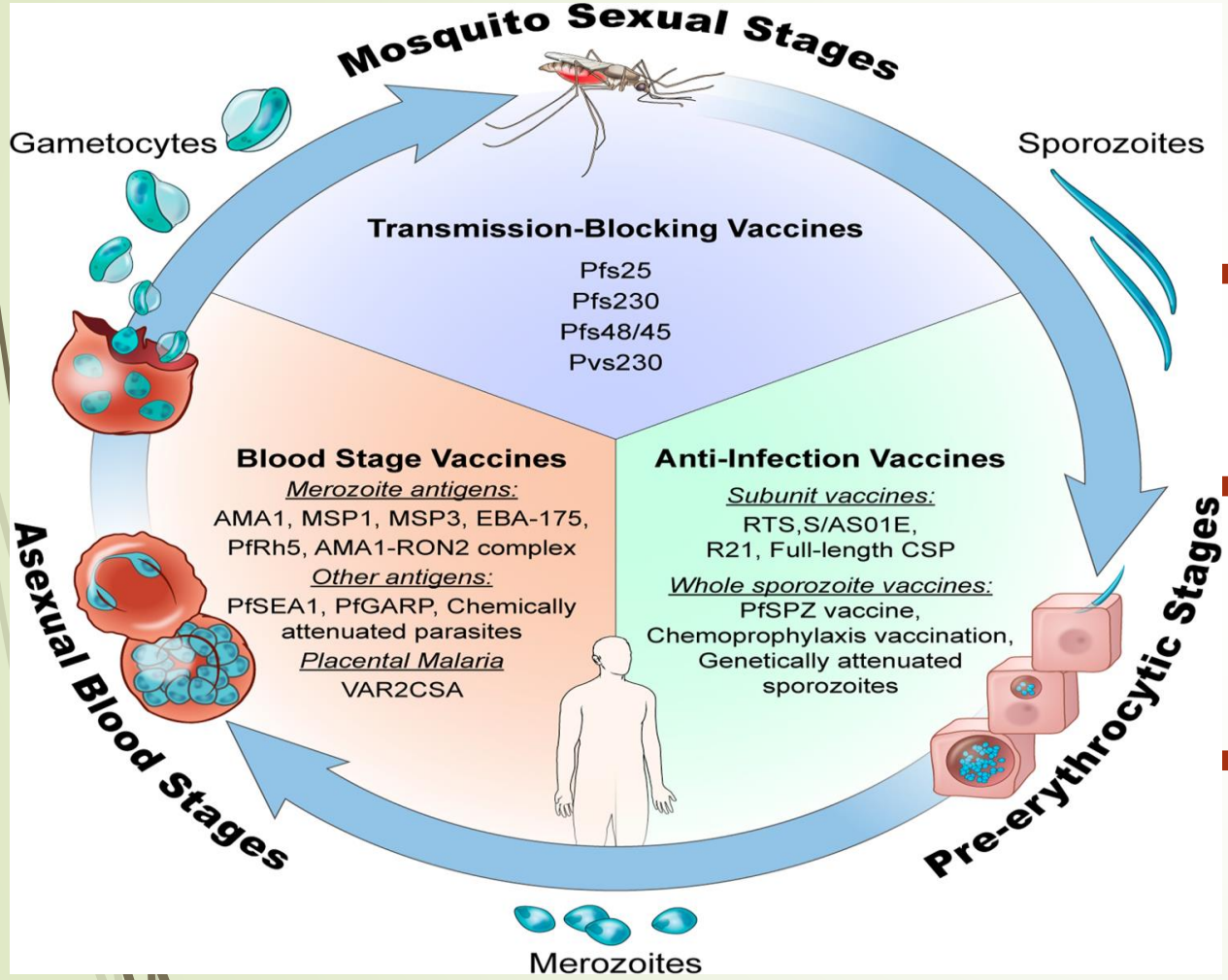


WHO report

> To reach global targets, African governments must harness innovation and this will require rapid expansion of new, innovative and impactful tools.

- Characteristics of the 32 malaria-eliminating countries are presented, and contrasted with countries that pursued elimination in the past.
- Challenges and risks of elimination are presented, including *Plasmodium vivax*, resistance in the parasite and mosquito populations, and potential resurgence if investment and vigilance decrease.
- The benefits of elimination are outlined, specifically elimination as a regional and global public good. Priorities for the next decade are described.

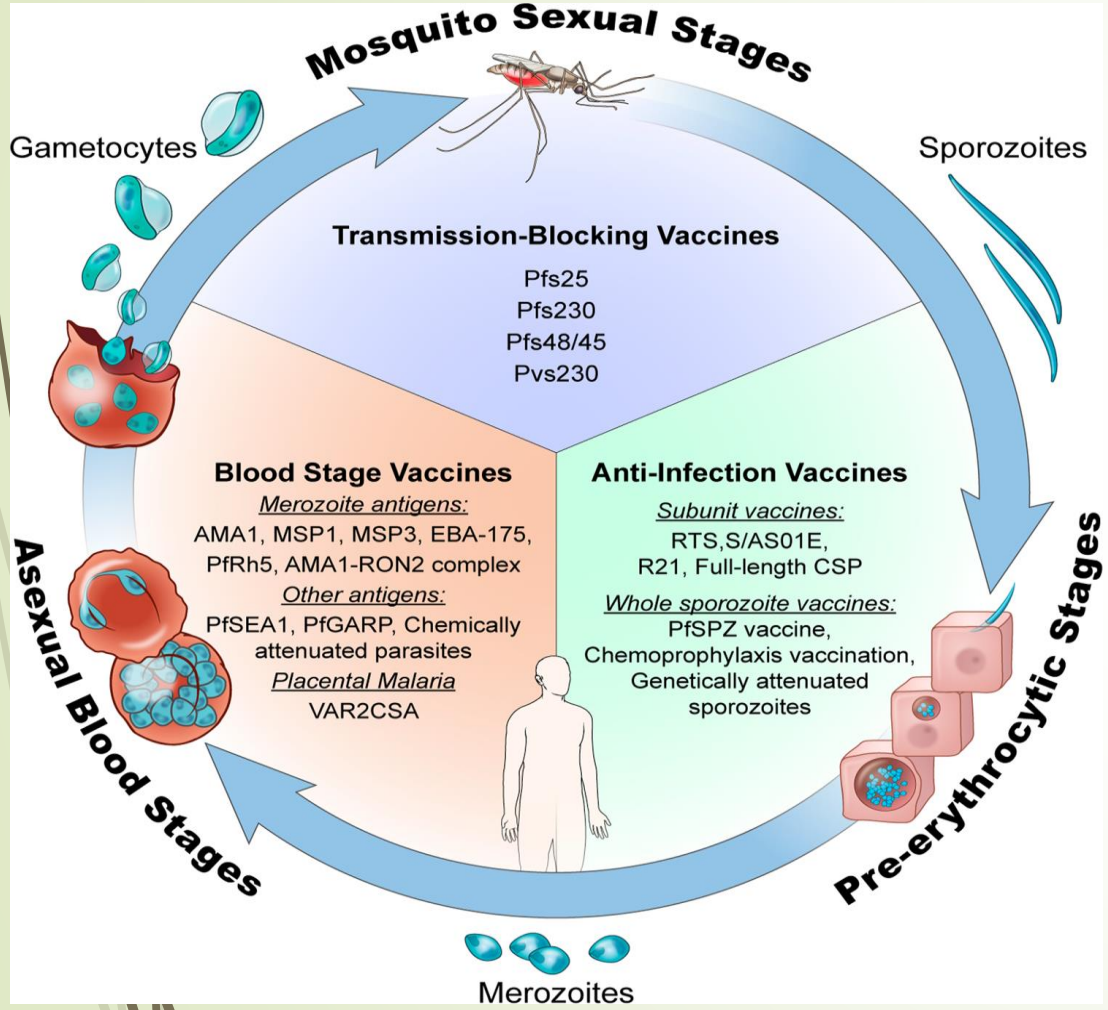
Key messages



- A three-part strategy is now agreed to move the world to eventual malaria eradication: aggressive control in the high-burden regions; elimination from the endemic margins inwards; and research and development into new interventions and technologies.
- 99 countries have endemic malaria; of these, 67 are controlling malaria and 32 are pursuing an elimination strategy.
- The 32 malaria-eliminating countries span all geographic locations, sizes, and incomes. Many of them have the prospect of eliminating malaria within the next decade.
- Countries contemplating elimination should comprehensively assess the feasibility of malaria elimination.

Taken from https://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2810%2961270-6/fulltext

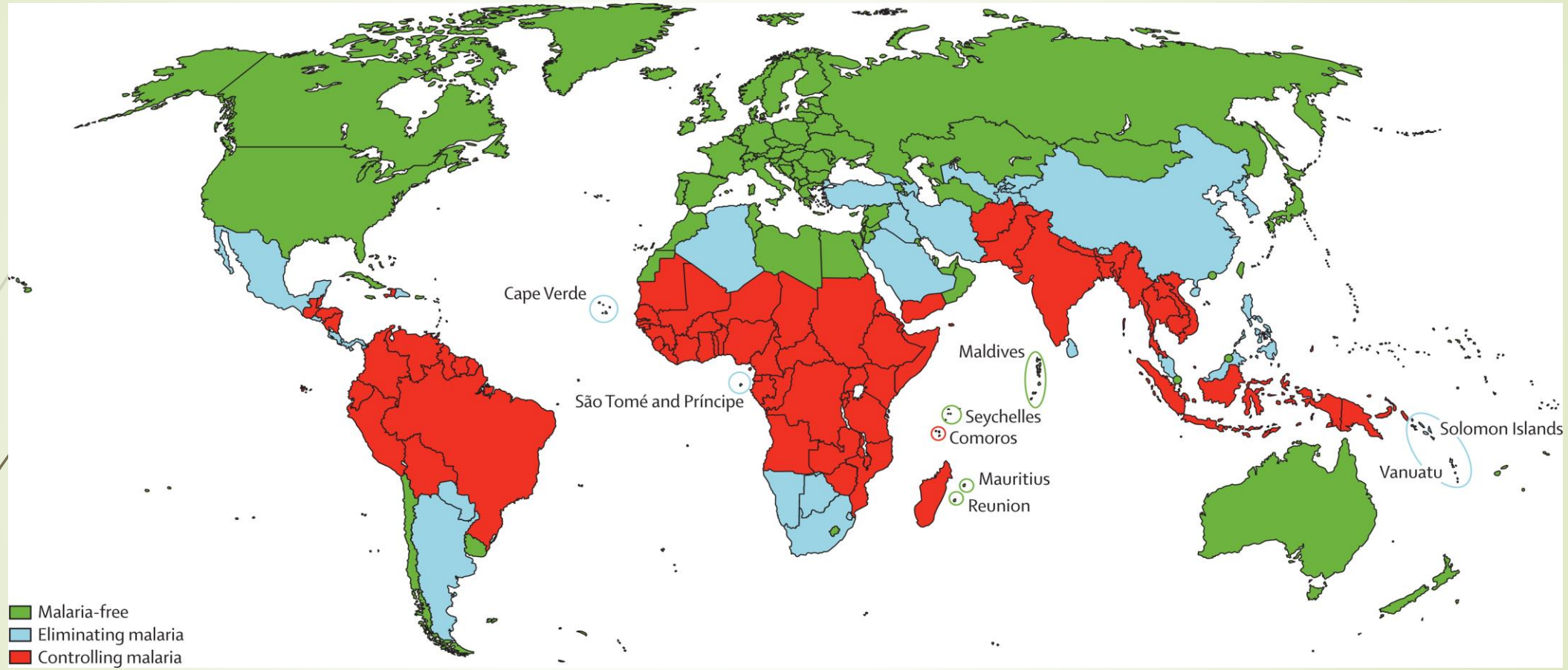
Key messages



Taken from https://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2810%2961270-6/fulltext

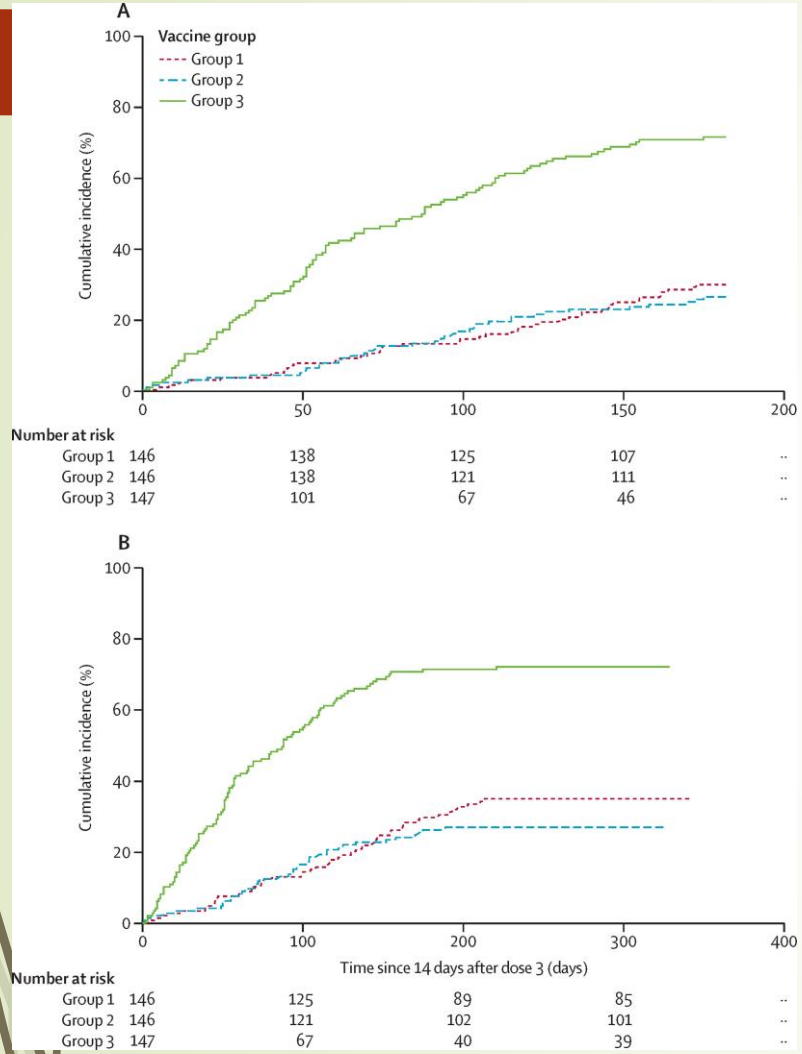
- 25 of the 32 malaria-eliminating countries are solely or mainly fighting a battle against *Plasmodium vivax* malaria. New interventions and techniques are urgently needed to detect and treat this infection.
- Although malaria elimination has risks, the alternative of maintaining controlled low-endemic malaria for a long period also has risks, many of them similar in nature and magnitude.
- The benefits of malaria elimination are not sufficiently understood, but include substantial positive externalities in the form of benefits to neighbouring countries (regional public goods) and worldwide (global public goods).
- Various overarching challenges exist, including improved methods for diagnosis and surveillance, multicountry collaboration, and ensuring long-term commitment and resources to achieve elimination and maintain it for decades thereafter.

Shrinking malaria world wide



Categorisation of countries as malaria free, eliminating malaria, or controlling malaria

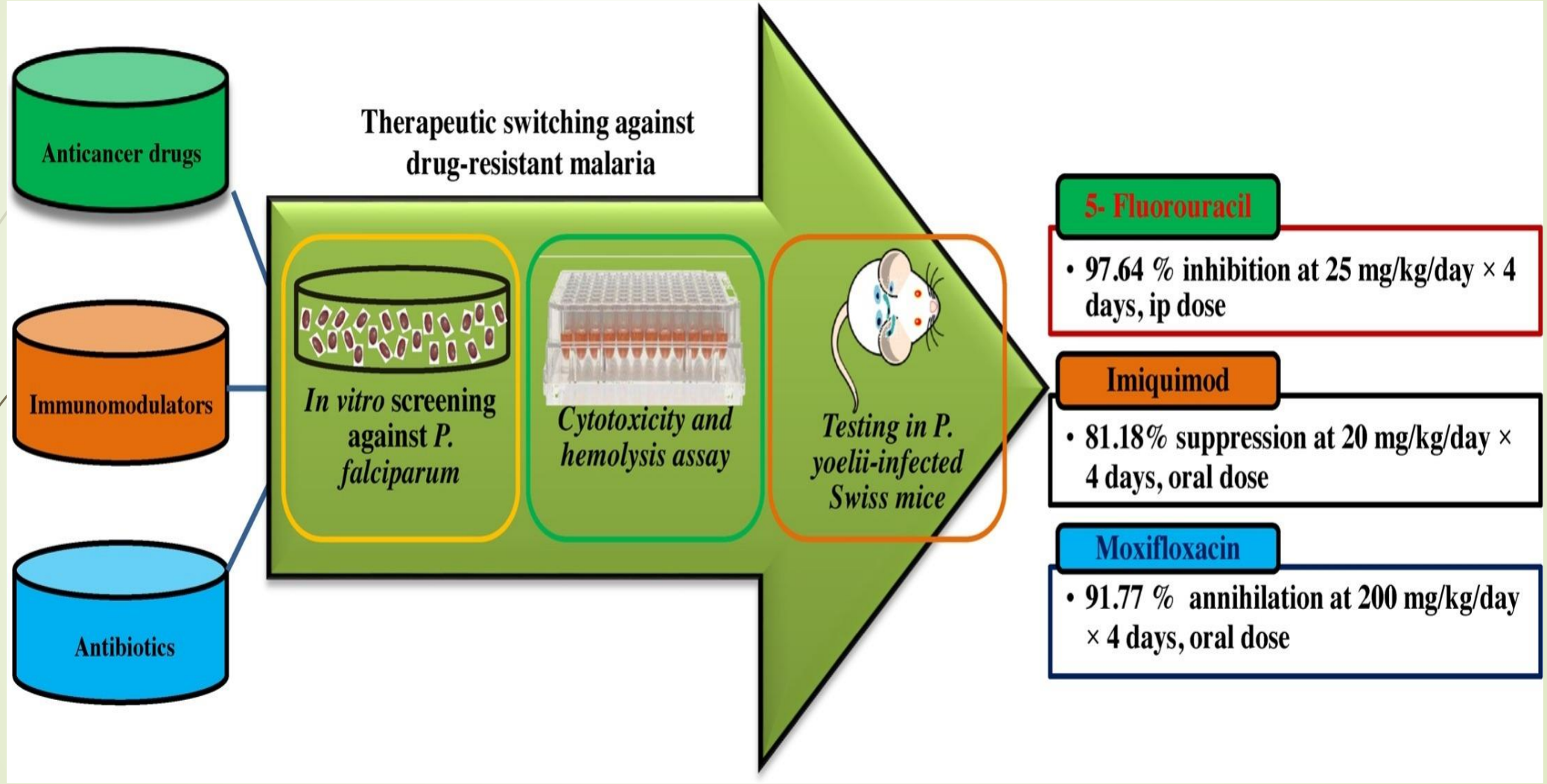
Recent trends in treatments of malaria



- Efficacy of a low-dose candidate malaria vaccine, R21 in adjuvant Matrix-M, with seasonal administration to children in Burkina Faso: a randomized controlled trial
- Mehreen S Datoo, MRCP * et al.
- Open AccessPublished:May 05, 2021DOI:https://doi.org/10.1016/S0140-6736(21)00943-0

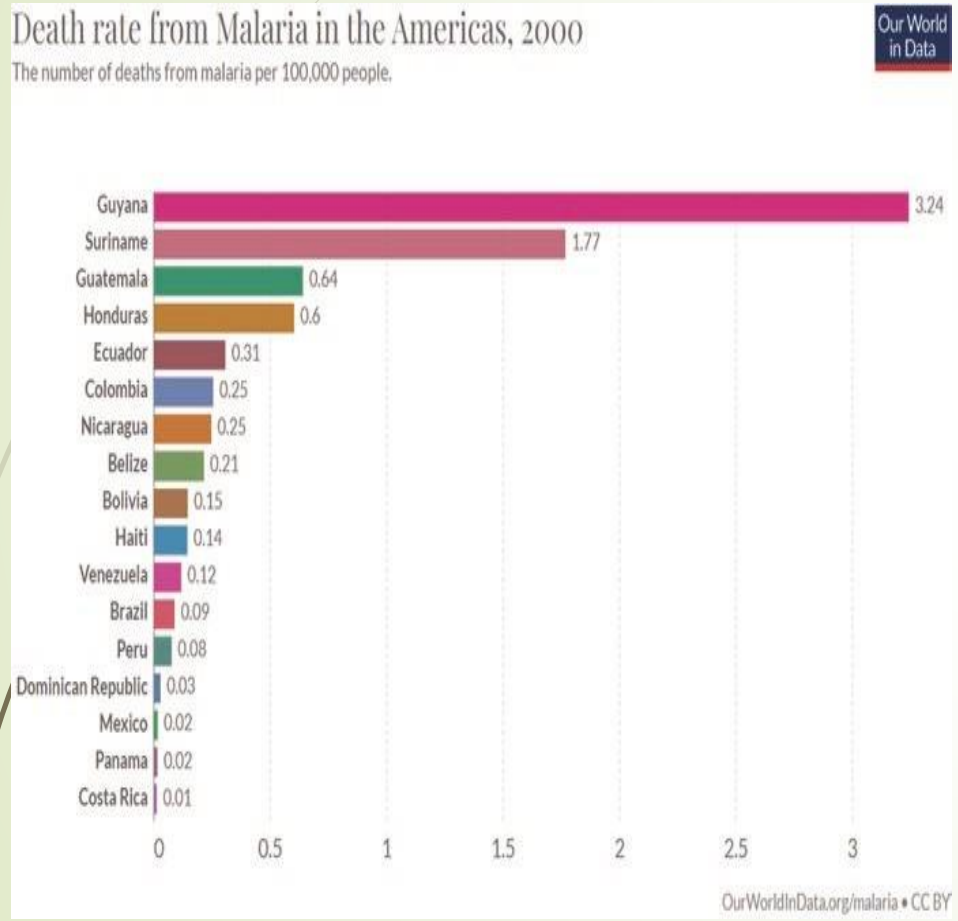
Kaplan-Meier estimates of the time to first episode of clinical malaria
The primary analysis was based on a modified intention-to-treat population. Group 1 received 5 µg R21/25 µg MM, group 2 received 5 µg R21/50 µg MM, and group 3, the control group, received rabies vaccinations (Rabivax-S). (A) Data beginning from 14 days to 6 months after third vaccination. (B) Data beginning from 14 days to 12 months after third vaccination. MM=Matrix-M.

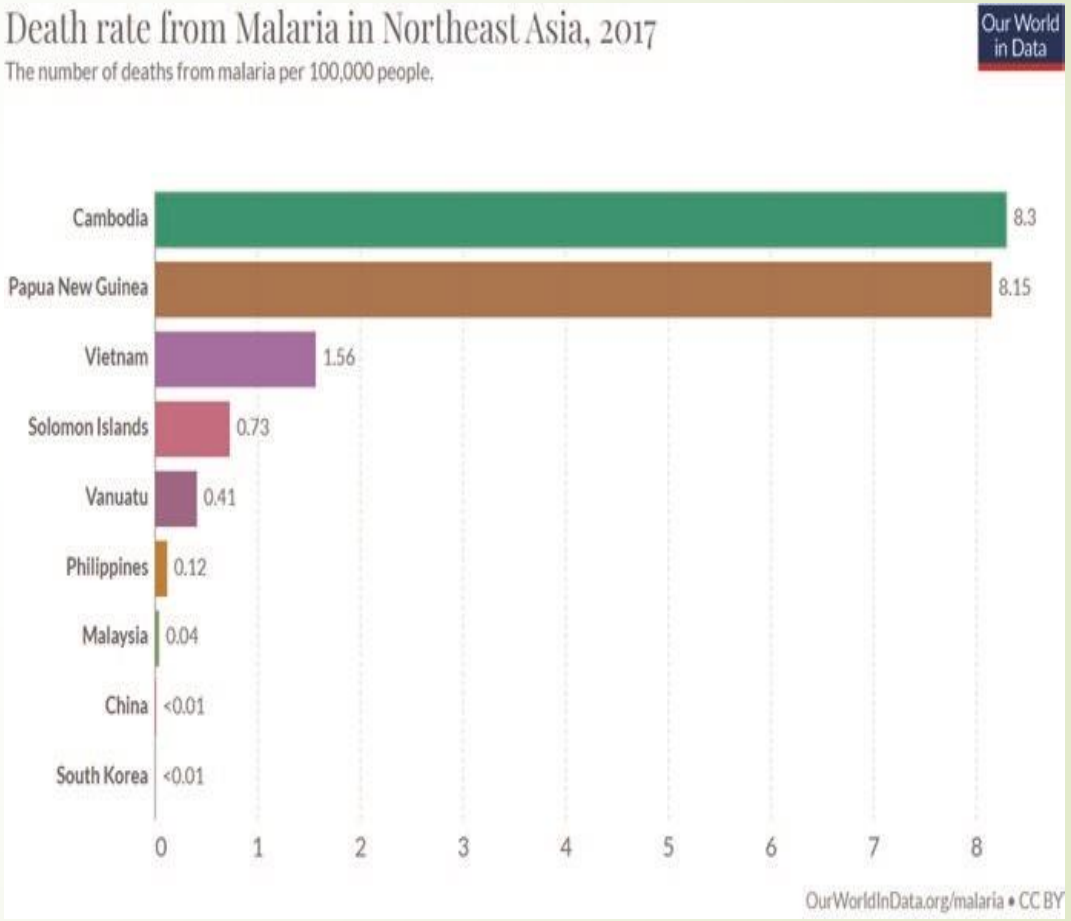
Therapeutic switching against drug resistant malaria



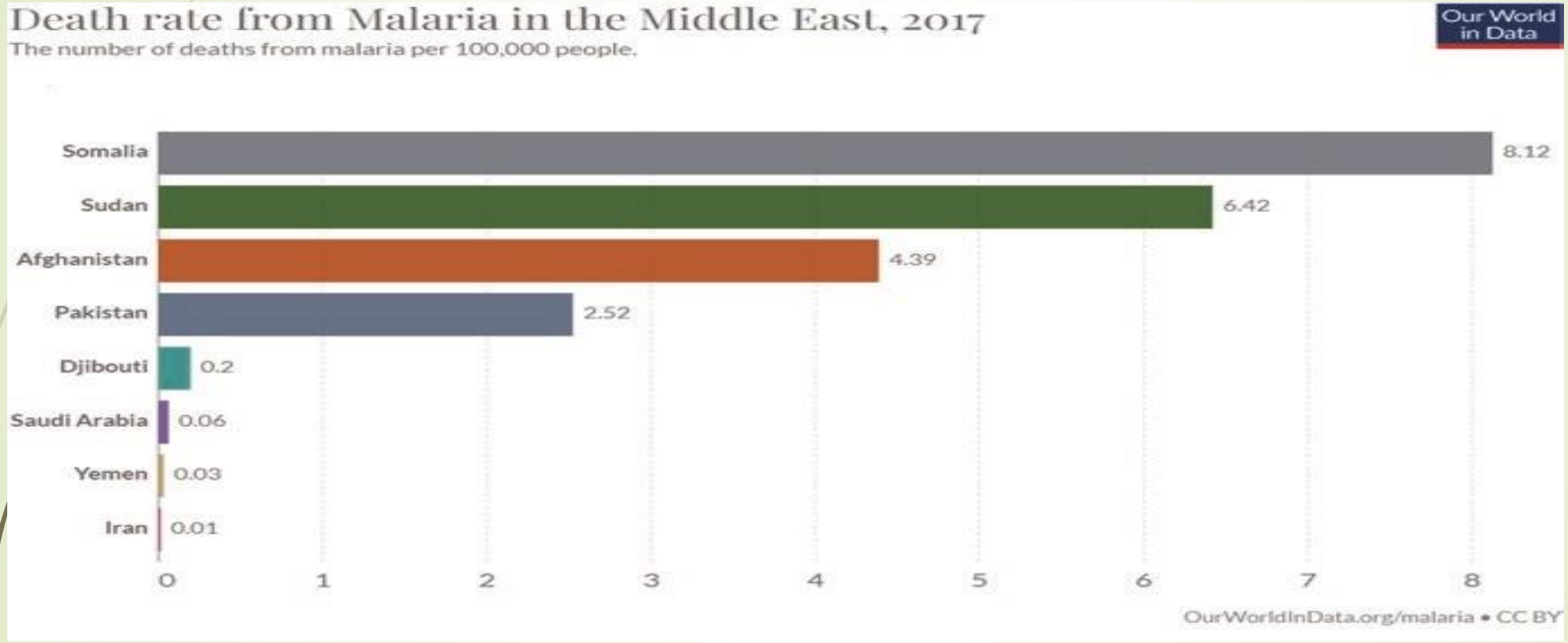
Taken from https://www.sciencedirect.com/science/article/pii/S0753332221000603

Death rate in different countries due to malaria

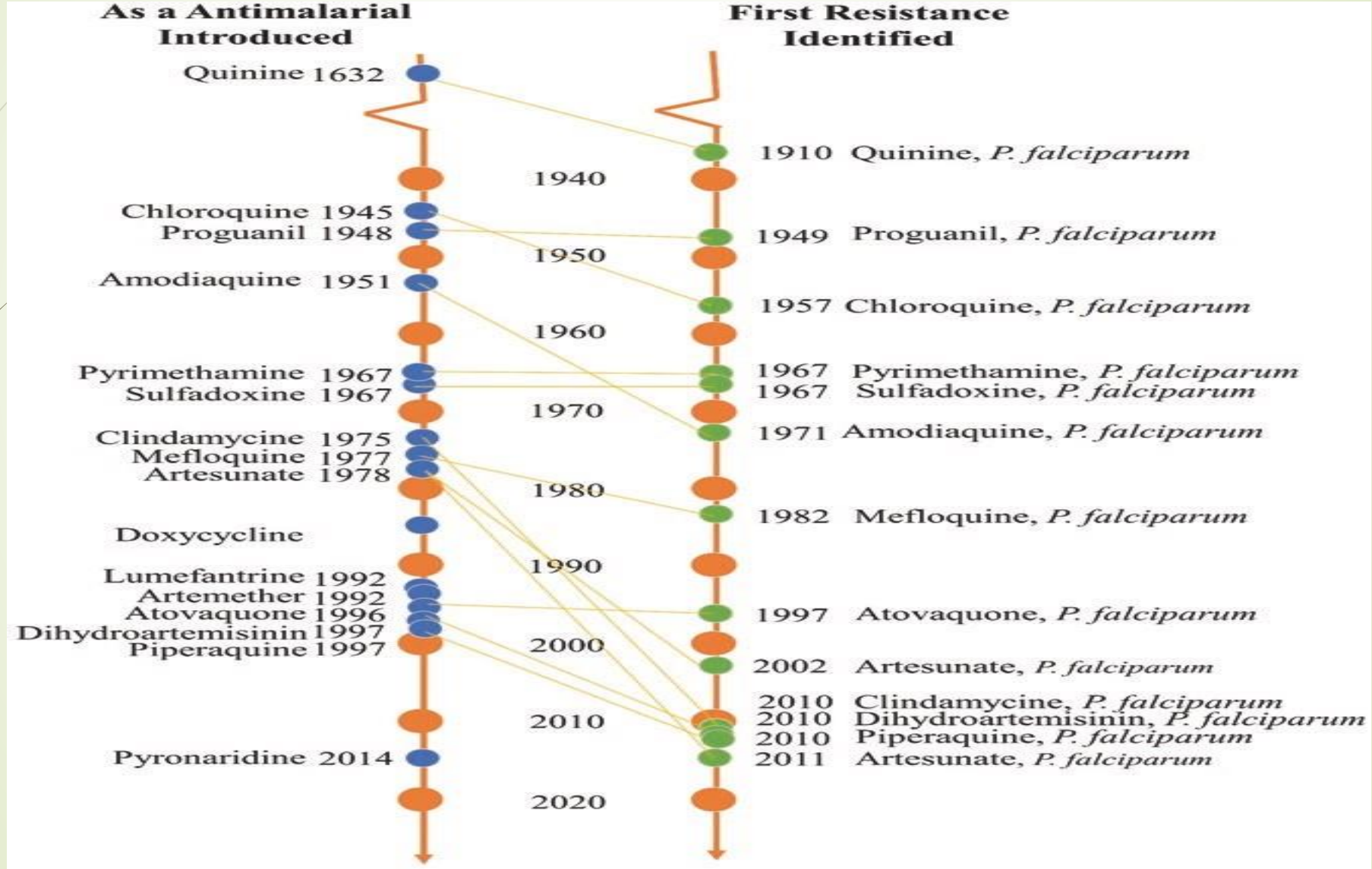




Death rates in Middle east



Time line for antimalarial drug resistance



New Drug Discovery and Development for antimalarial drugs

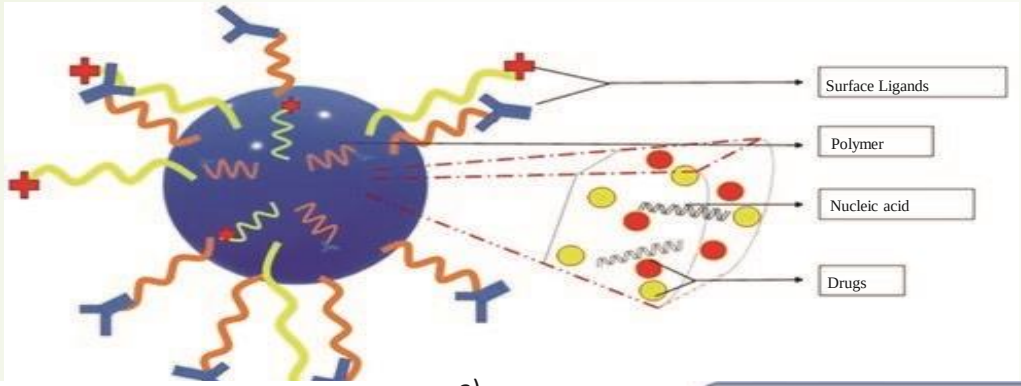
- Additional approaches to developing strong antimalarial medications include rational targeting of critical parasite activities (target-based) and whole-cell phenotypic screening for chemicals that have desired effect on parasite cells.
- The crucial targets include metabolite biosynthesis, membrane transport, and signaling system, and the hemoglobin degradation processes
- KAI407, 0KAF156, plasmodium phosphatidylinositol-4-OH kinase inhibitors, KAE609, *P. falciparum* P-type ATPase 4 inhibitors, and DDD107498 are some of the new antimalarial compounds discovered using a cell-based approach
- In contrast, Plasmodium DHODH inhibitor, DSM265, a compound with multistage antimalarial activity and the inhibitor of DHFR and P218 are the potent parasite inhibitors found from target- based screening techniques

Formulations products currently available in market

Active ingredients	Dosage form	Dosage
Artemether-lumefantrine (AL)	Tablet/dispersible	20 mg artemether + 120 mg lumefantrine
	Tablet	40 mg artemether + 240 mg lumefantrine
Artesunate + amodiaquine	Tablet	25 mg artesunate + 67.5 mg amodiaquine 50 mg artesunate + 135 mg amodiaquine 100 mg artesunate + 270 mg amodiaquine
Artesunate + mefloquine	Pediatric tablet	25 mg artesunate + 55 mg mefloquine hydrochloride (equivalent to 50 mg mefloquine base)
	Adults tablet	100 mg artesunate + 220 mg mefloquine hydrochloride (equivalent to 200 mg mefloquine base)
Artesunate + sulfadoxine-pyrimethamine	(No fixed dose combination)	Scored tablets containing 50 mg artesunate and fixed dose combination tablets comprising 500 mg sulfadoxine + 25 mg pyrimethamine
Dihydroartemisinin + piperaquine	Pediatric tablet	20 mg dihydroartemisinin + 160 mg piperaquine
	Adult tablet	40 mg dihydroartemisinin + 320 mg piperaquine

Some new trends developing nano drug delivery systems to treat malaria

- Polymeric nanoparticles to treat malaria



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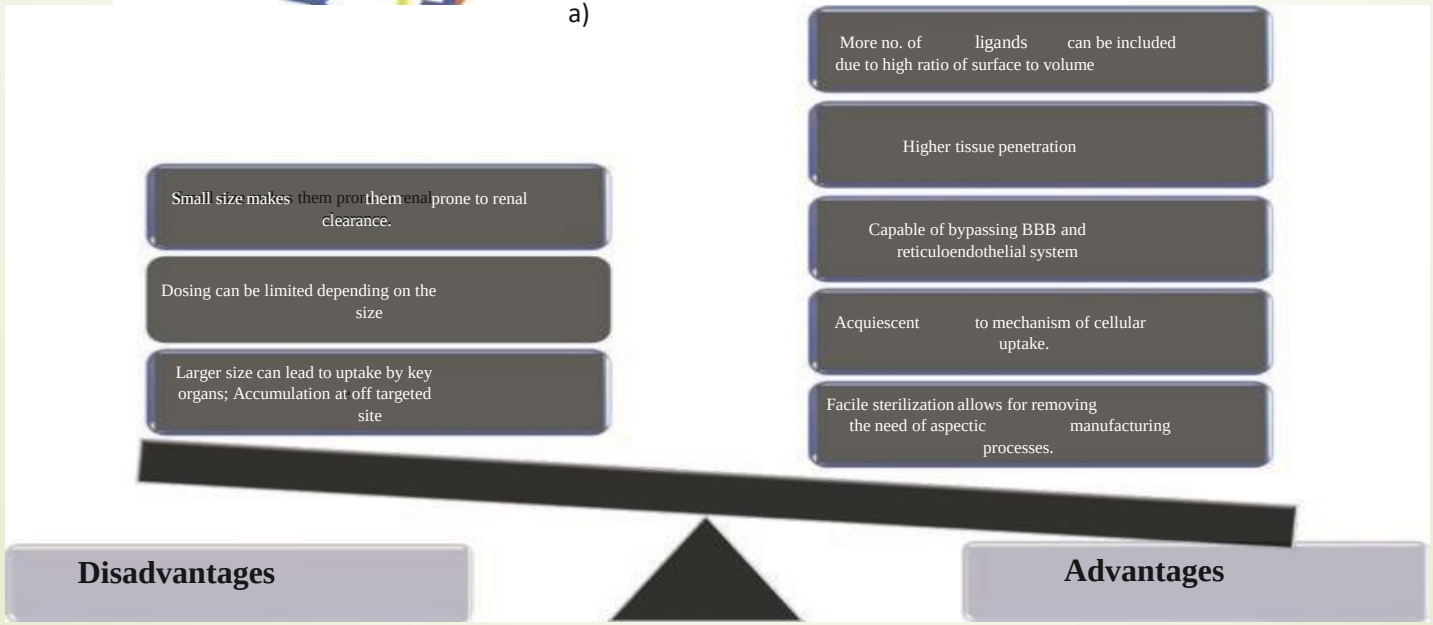
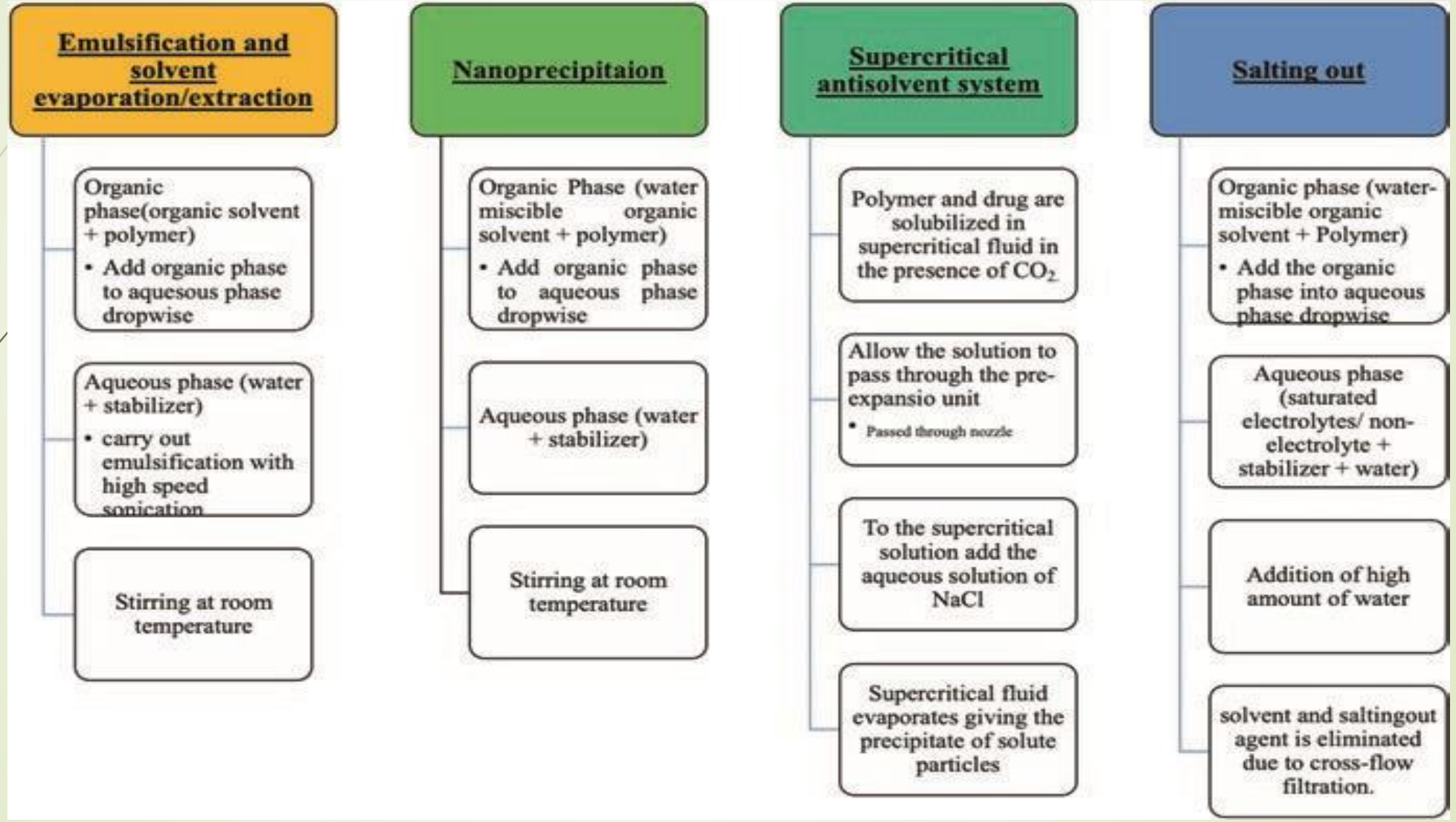
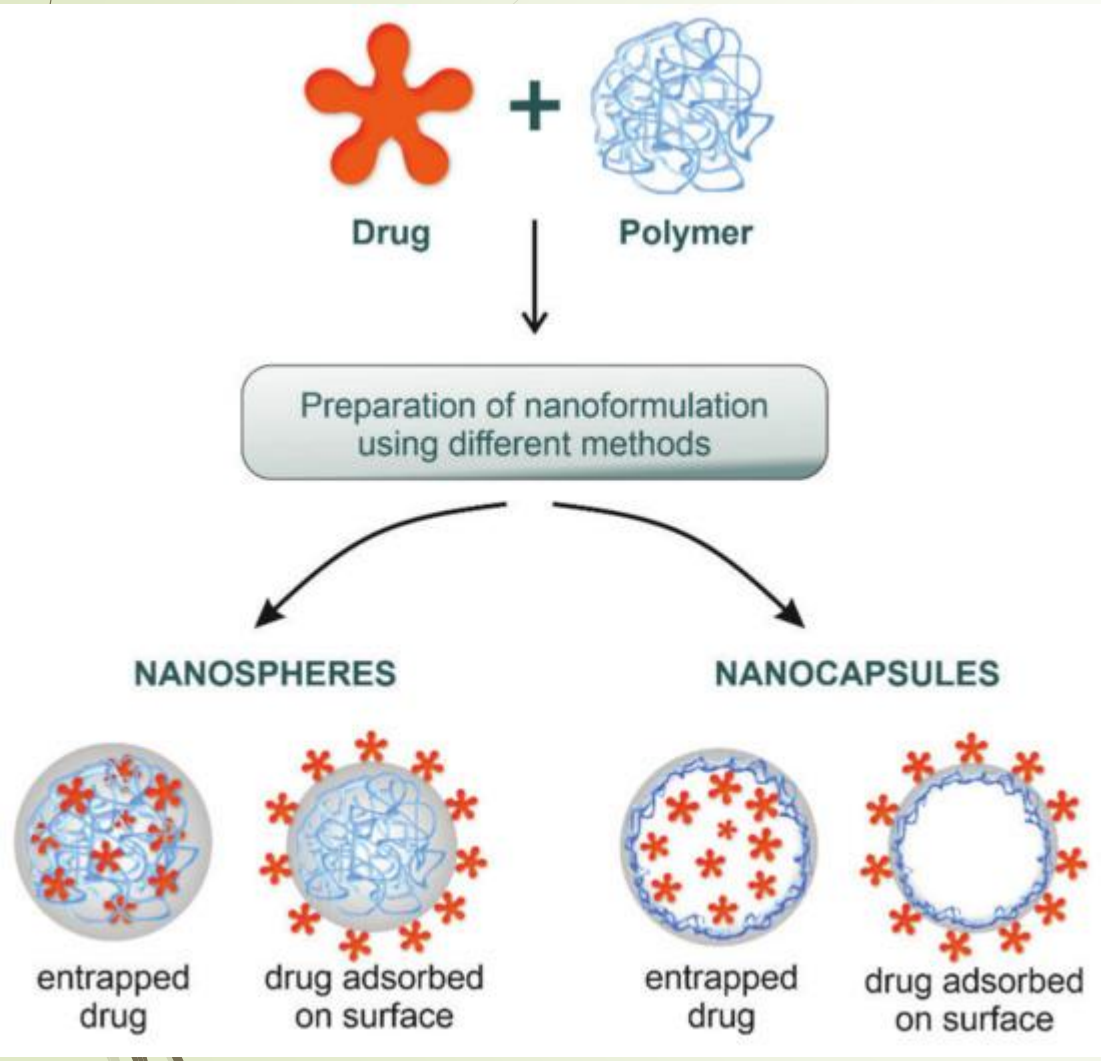


Various methods to prepare polymeric nanoparticles



Drugs used to treat malaria using polymeric nanoparticles

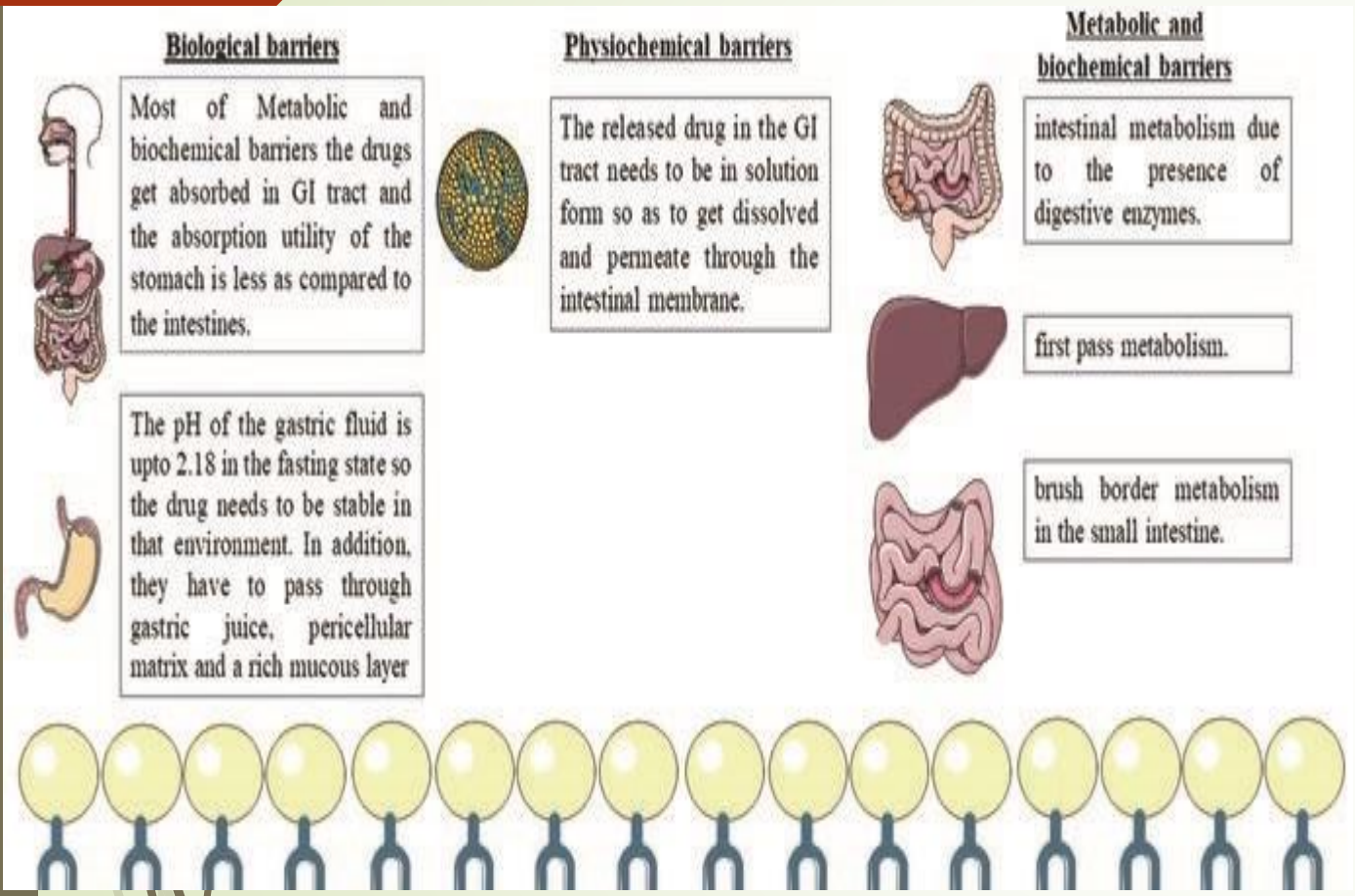


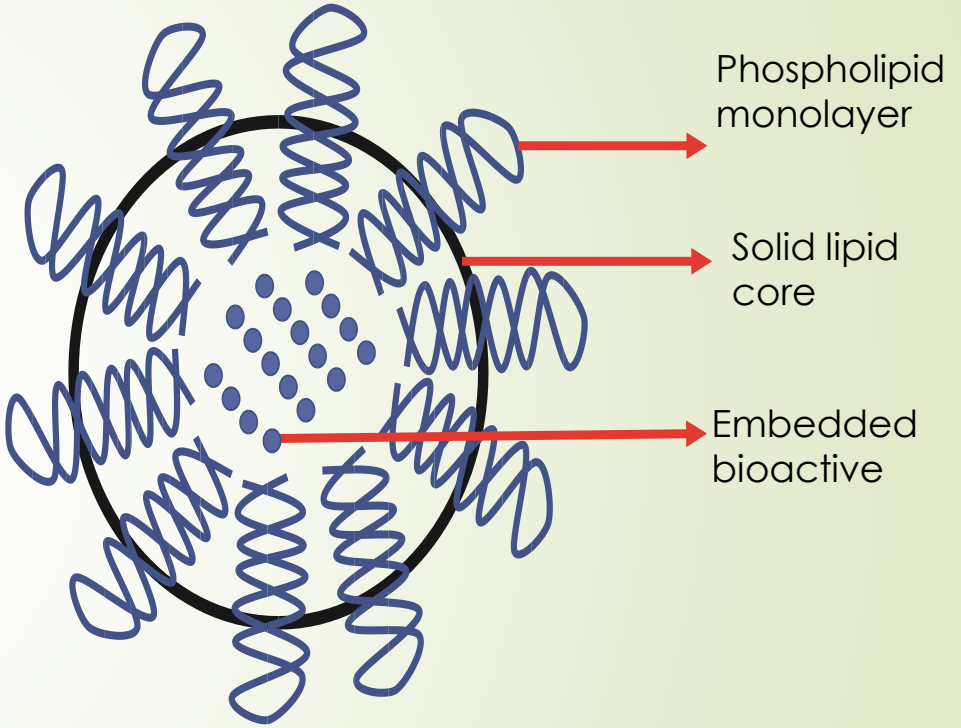
- **Artemether:** Artemether (ART) is a methyl ether derivative of dihydroartemisinin which is considered to be effective in reducing mortality due to severe malaria
- **Artesunate:** Artesunate is a partial synthetic derivative of artemisinin. Artesunate has a short half-life which requires its frequent administration. A lower parasite suppression was found concerning free artesunate.
- **Dihydroartemisinin** : Dihydroartemisinin (DHA) is known to be one of the earliest identified derivatives 278 of artemisinin with substantial antimalarial activity used PLGA, PEG nanoparticles
- **Lumefantrine**: Lumefantrine was previously known as benflumetol, which is an antimalarial drug 313 belonging to the phenanthrene class which is known to be effective against all 314 malarial used Hydroxy propyl methyl cellulose (HPMC polymers) for drug delivery

Drug combinations used for delivery of antimalarial nanoparticles drugs

Drug combination	Polymers used	Route of administration	Physicochemica characterization	Significant outcomes
Pimaquine and dihydroartemisinin	Substituted polyphosphagzenes	Intravenous	130 to 180 nm particle size	Rapid uptake of drugs and prolonged action
Dihydroartemisinin and Chloroquine Phosphate	Polycaprolactone	oral	450 nm	Temperature and time dependent release
Curcumin and artesunate	PLGA	Oral	250 nm	Better antiplasmodial activity
Artemether and Lumefantrine	Chitosan	Trandepidermal	110 nm	Alternative route for delivery
Artemether and Lumefantrine	Soy lecithin and cjolesterol	Ether injection method	125 nm	Low toxicity, biocompatibility and tissue uptake
Chloroquine Phosphate and azithromycin	PLGA	Double emulsion oral	90 nm	Synergistic action and overcoming drug resistance

Solid lipid nanoparticles for Treatment of malaria



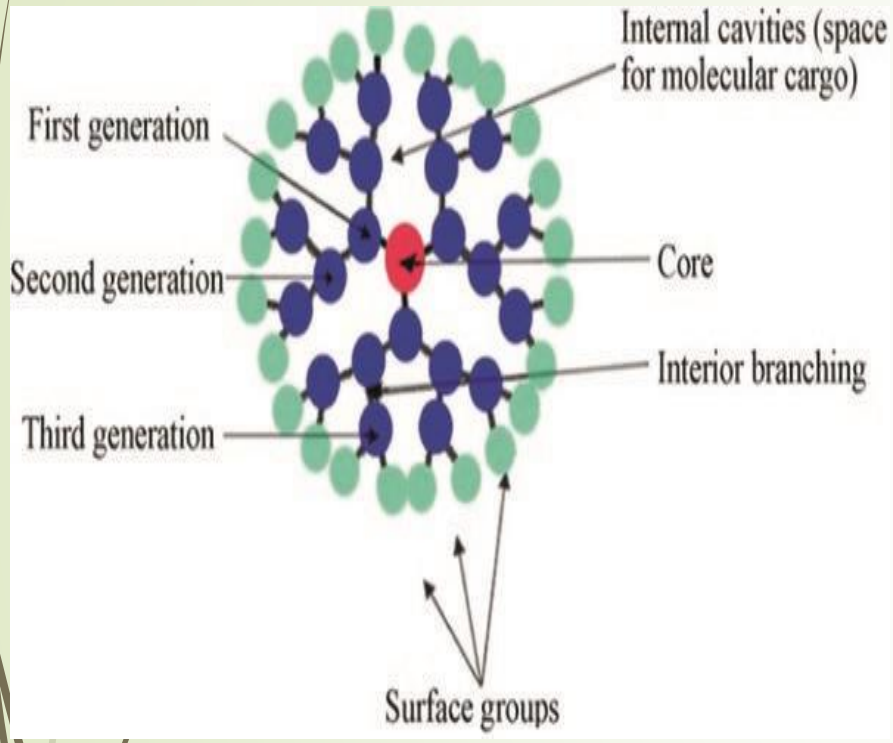


Solid lipid nanoparticles for Treatment of malaria

- Commonly used antimalarial drugs tried for nano SLN drug delivery

Drug combination	Polymers used	Route of administration	Physicochemica characterization	Significant outcomes
Chloroquine	Modified double emulsion	oral	375 nm	Solubility enhancement
Primaquine	W/O double emulsion	oral	240 nm	Higher antimalarial efficiency
Dihydroartmisinin	Solvent diffusion method for lipids	Oral	200 nm	Longer duration of action
Artemether	High shear homogenization	Oral	365 nm	Solubility enhancement
Lumefantrine	Ultra sonication	Oral	350 nm	Enhanced oral bioavailability
Curcuminoids	High shear homogenization	Oral	120 nm	Improved bioavailability and localization
Zataria multiflora essential oil	High shear homogenization	Oral	135 nm	High protection against Annapolis stephensi

Dendrimers as potential carriers for antimalarial drugs

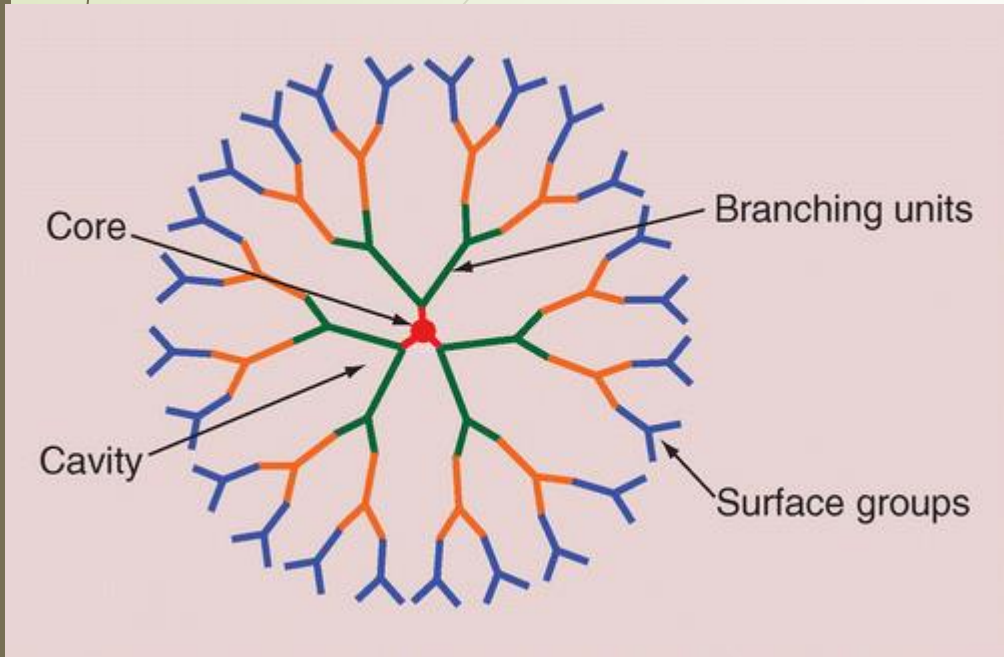


Common structure of dendrimers

Types of dendrimers	Examples
PAMAM (poly(amidoamine))	Tomalia
Frechet type	Tomalia
PPI (poly(propylene imine))	Astramol
Core shell tecto	Starburst
Chiral	Pentaerythritol derivatives
Liquid crystalline	Mesogen-functionalized carbosilane
Peptide	Beta casomorphin
Glyco	Glycodendrimersome
Hybride	Polysisesquioxanes
PAMAMOS (poly(amidoamine-organosilican))	Silarylene-siloxane
Amphiphilic	SuperFect, Bola-amphiphiles

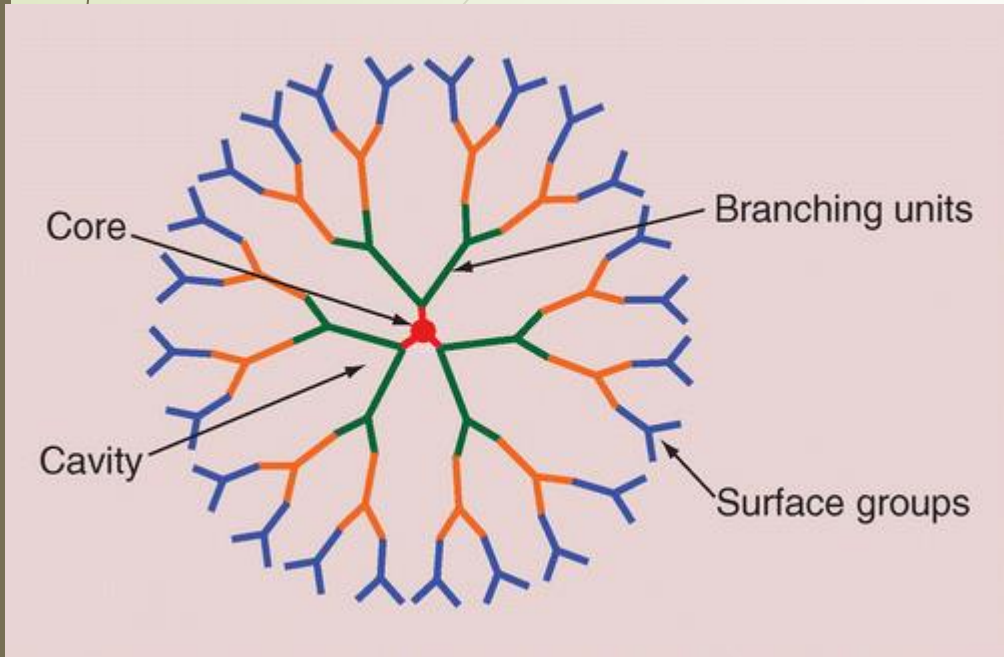
Types and examples of Dendrimers

Dendrimers for carriers for antimalarial drugs



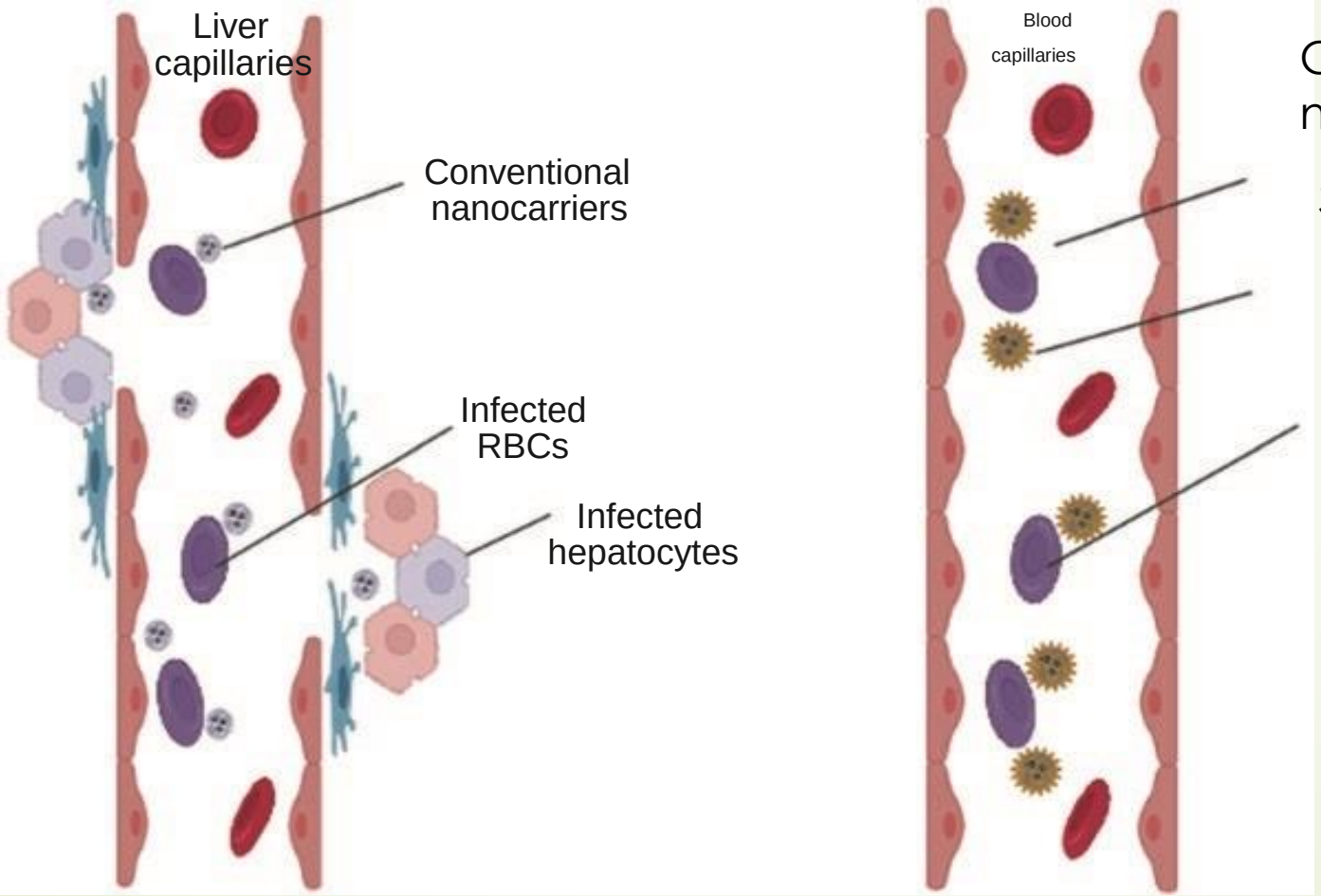
- Recently, dendrimers have been studied for the management of malaria. In a study of Bhadra et al., poly-L-lysine-based peptide dendrimers with a PEG amine core (5G) coated with chondroitin sulfate A (CSA) were used to get a controlled and extended release of chloroquine phosphate (CQ) [103]. The following chart shows a brief process of production.
- Chiloquin was used as antimalarial drug in dendrimers showed promising applications , still under study.
- Movellan et al. evaluated encapsulation of antimalarial drugs. They used four different dendritic derivatives based on 2,2-bis(hydroxymethyl) propionic acid (bis- MPA) monomers. They studied chloroquine (CQ) and primaquine (PQ).

Dendrimers for carriers for antimalarial drugs



- Janus dendrimers A and B were synthesized by copper catalysed 1,3-dipolar azide- alkyne cycloaddition of the azido-terminated glycine containing dendron and the alkyne-terminated stearic acid-functionalized dendron. A and B were obtained with total yields of 16% and 3%, respectively.
- Hybrid dendritic-linear-dendritic block copolymers C and D were prepared from the commercial amphiphilic block copolymer Pluronic F127. The oil/water method, based on the emulsification of an organic phase including the corresponding dendritic derivative (compound A, B, C or D) and an aqueous phase including the drug, chloroquine (CQ) or primaquine (PQ), or rhodamine B, was used to form the nanovectors

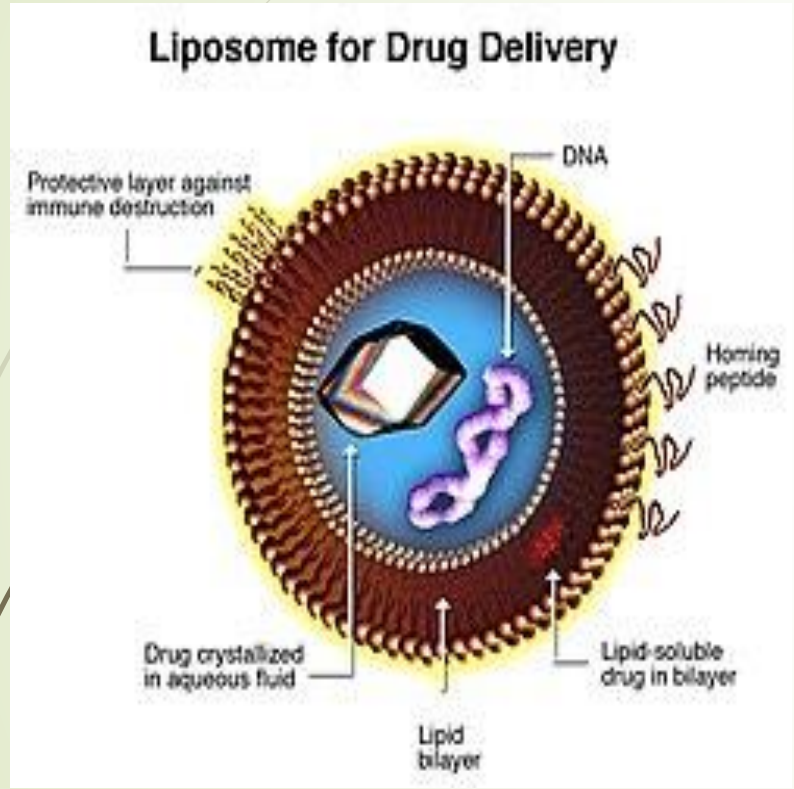
Liposomal drug delivery for antimalarial drugs



Conventional nano carriers

Surface modified nano carriers

Liposomal drug delivery for antimalarial drugs

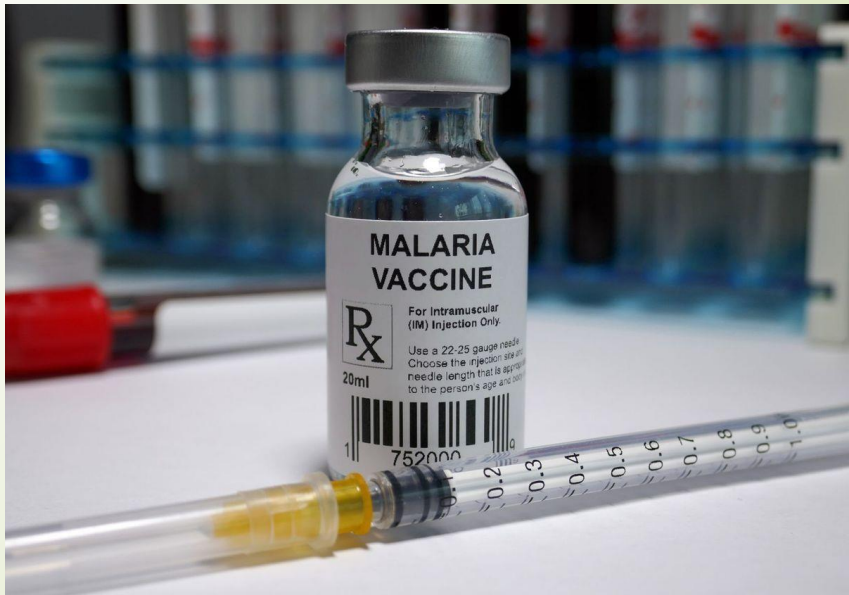


- Some of the efforts done in this regards include:
- Applications of Liposomes
- Conventional and long circulating neutral Liposomes
- Negatively charged Liposomes
- Targeted Liposomes for Antimalarial
- Peptide coated Liposomes for targeting Antibody mediated liposomes
- Liposomes as adjuvants for malarial vaccines
- Liposome based vaccines for Sporozoite Stage malaria
- Liposome based vaccines for Meorozoite Stage malaria
- Liposome based vaccines for Zygotes and Ookinetes stage malaria

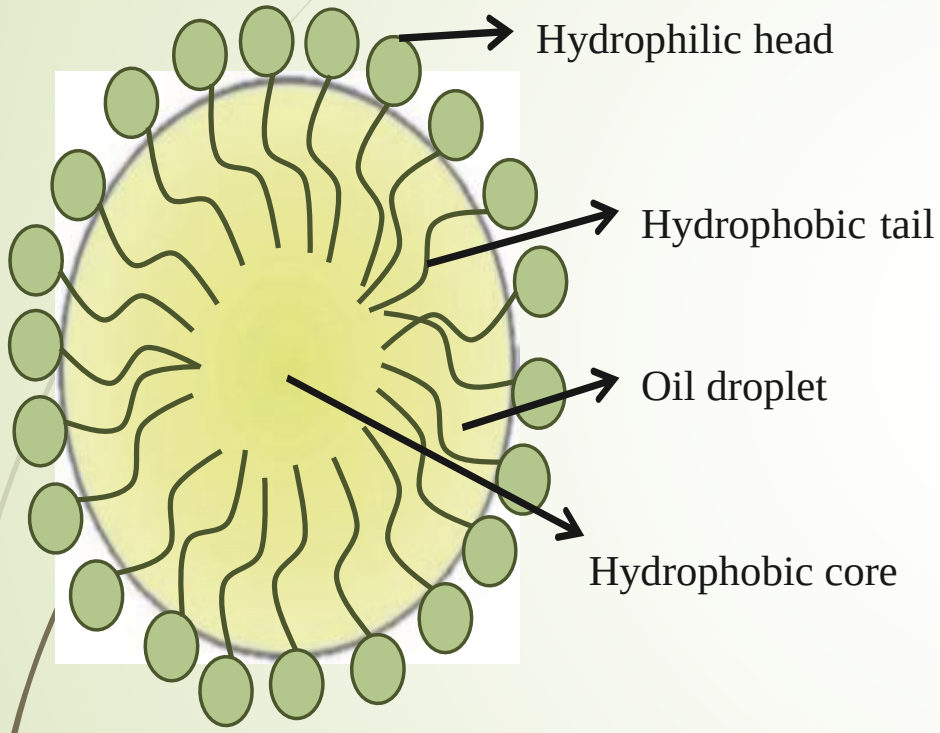
Liposomal drug delivery for antimalarial drugs

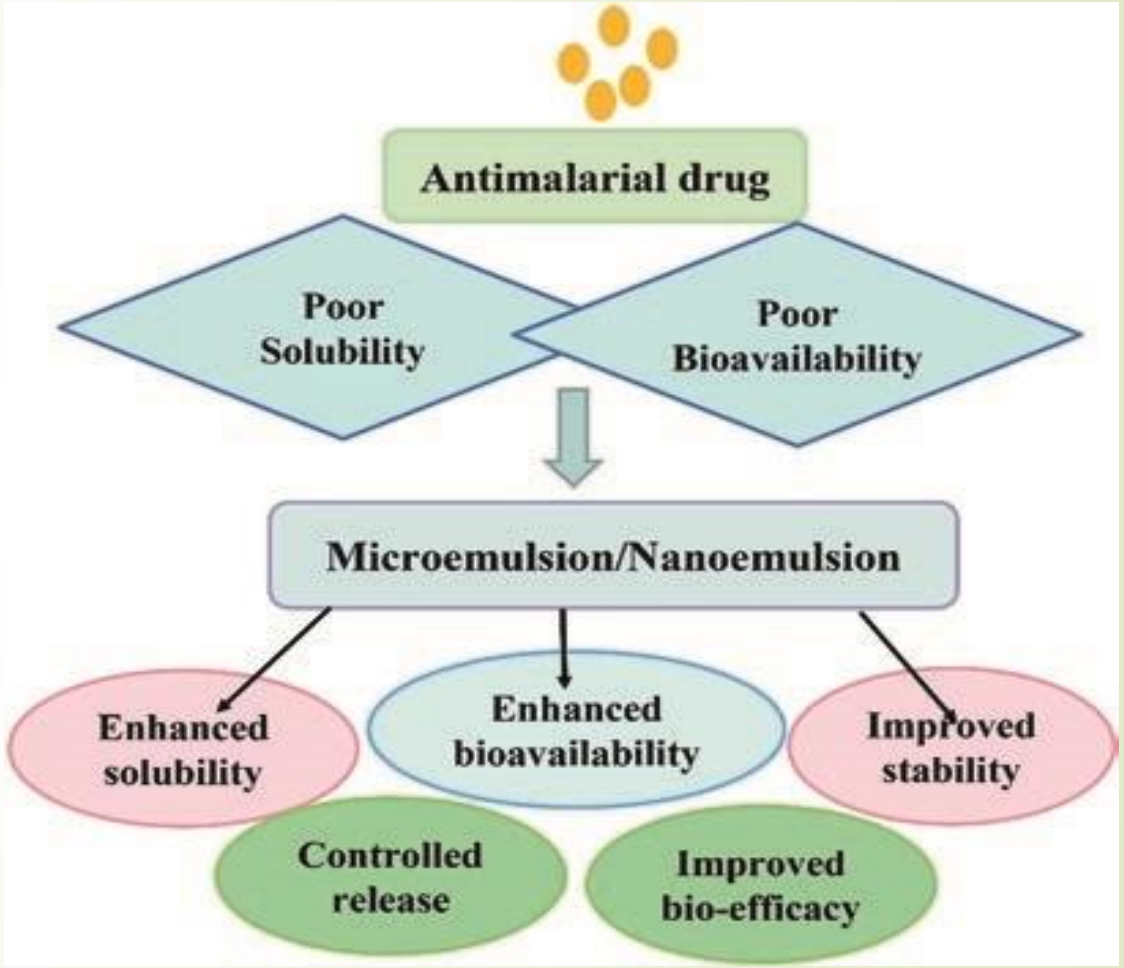
Form	Life Cycle Stage	Vaccine Strategy
✧ Sporozoite 	✧ Transmitted by mosquitoes ✧ Infects liver hepatocytes ✧ Develops into thousands of merozoite forms	✧ Vaccines targeting sporozoites or infected hepatocytes aim to prevent infection
✧ Merozoite 	✧ Released into blood stream ✧ Replicates in red blood cells ✧ Exponential rise in parasitemia associated with clinical illness	✧ Vaccines targeting merozoites or infected red blood cells aim to reduce disease severity
✧ Gametocyte 	✧ Some merozoites instead develop into gametocytes ✧ Can be taken up by a feeding mosquito and transmitted	✧ Vaccines targeting gametocytes aim to block transmission in a population

- **Antigens** explored for Antimalarial vaccines :
- FMP 013 and FMP 014
- PfMSP -1
- Pf 25
- RTS,S
- R32 NS 1
- R 32 tet



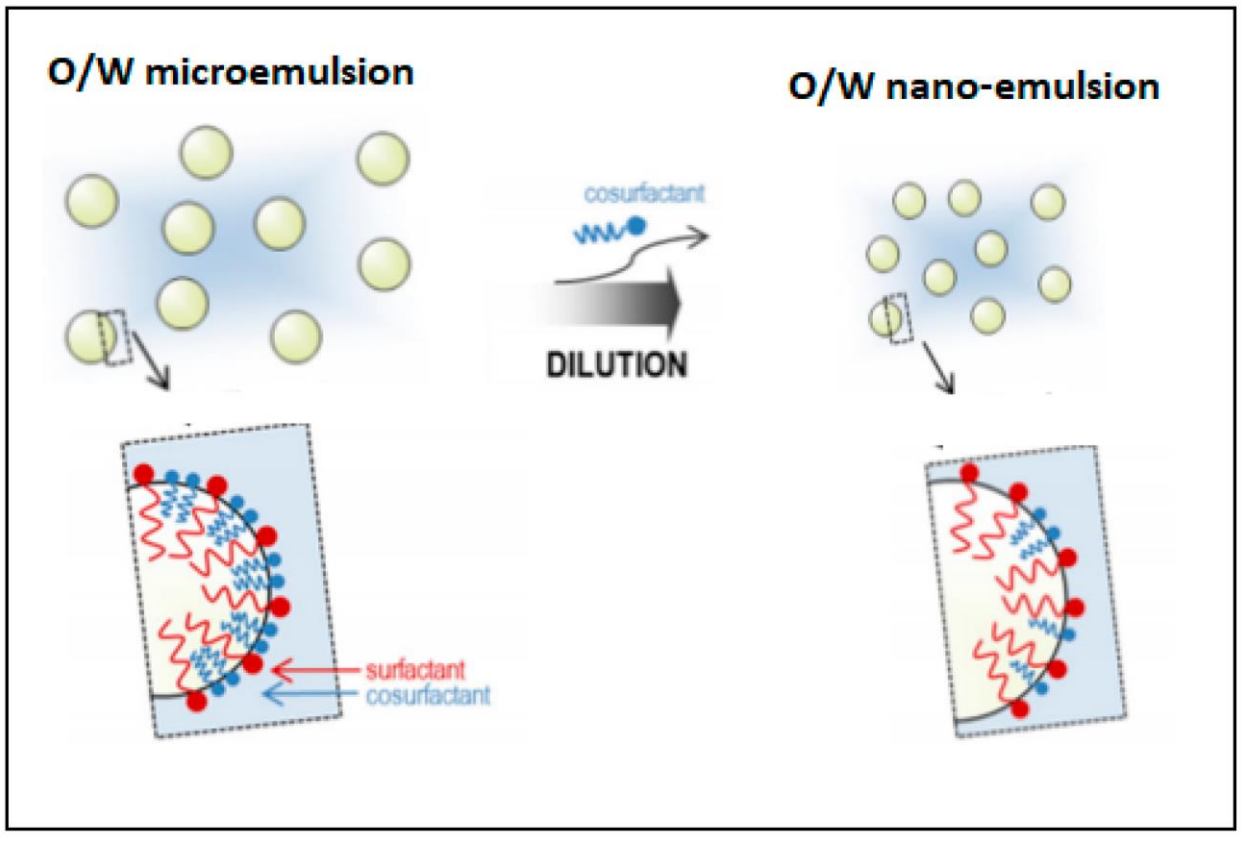
Potential of micro/nano emulsions for antimalarial drugs





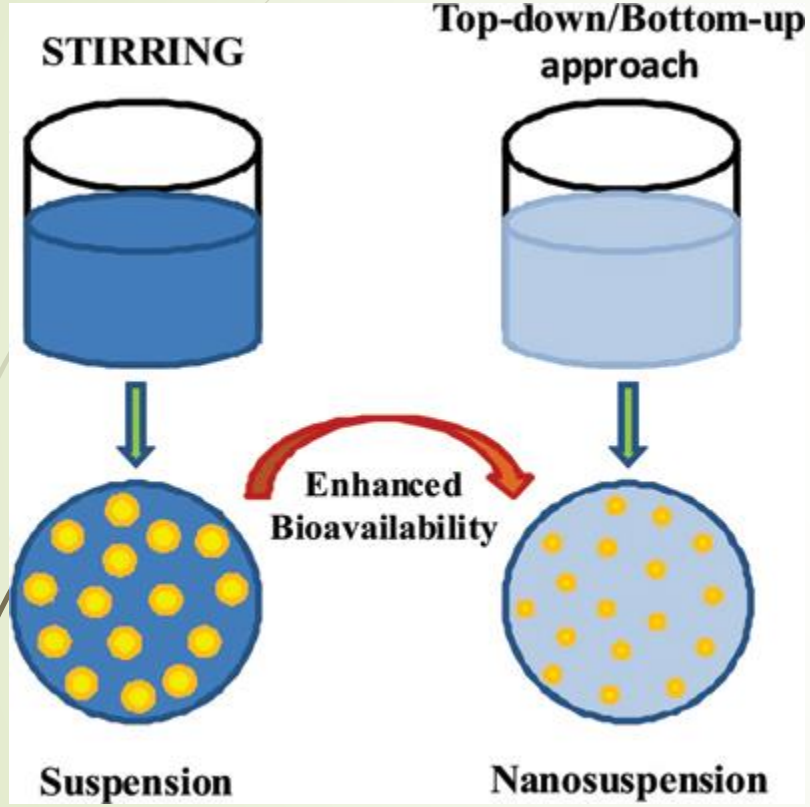
Challenges with Antimalarial drugs??

Potential of micro/nano emulsions for antimalarial drugs



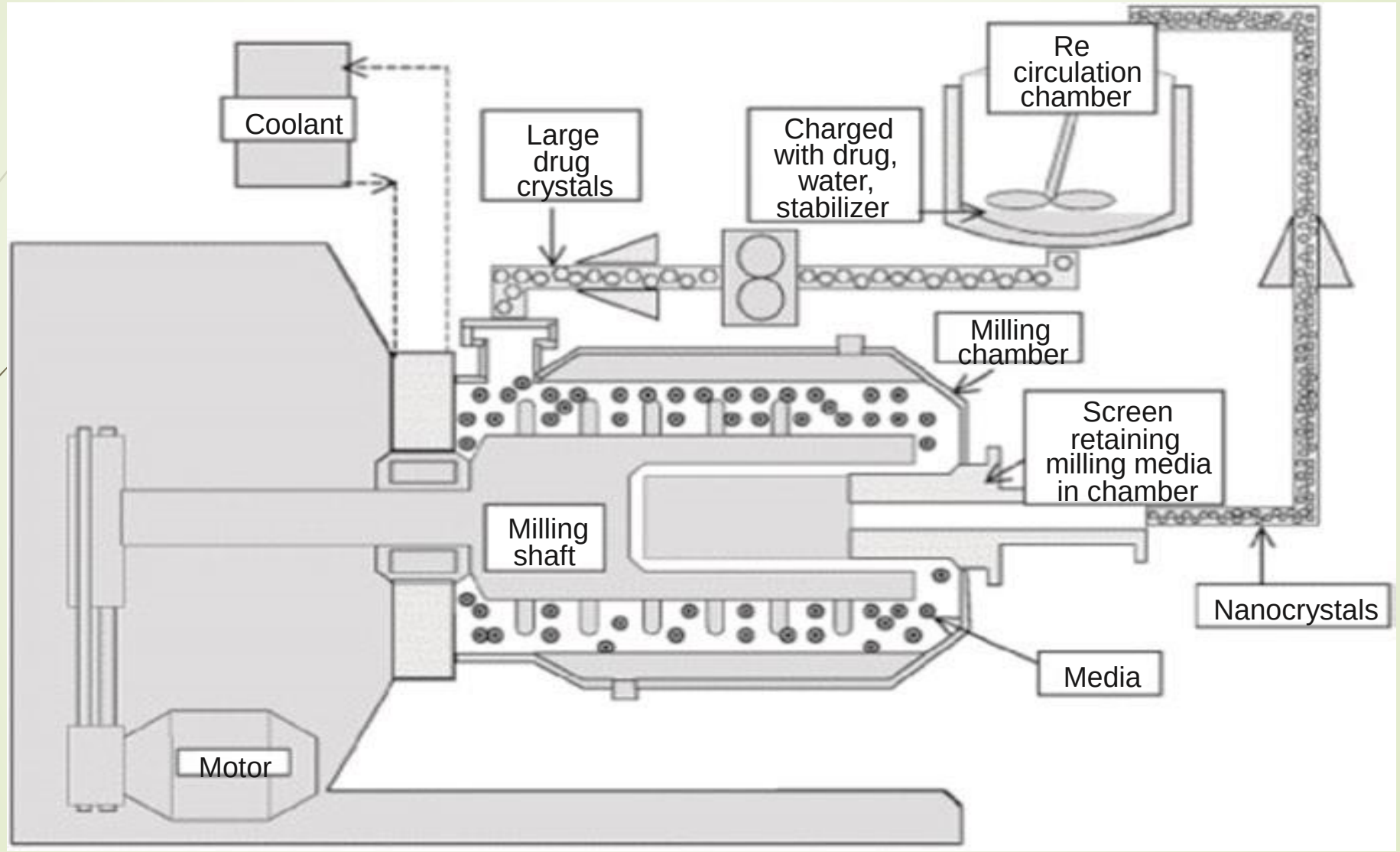
- Some Antimalarial drugs tried in micro / nano emulsions
- Cinchona alkaloids
- Quinoline methanols
- 4-Aminoquinolines
- 8 Aminoquinolones
- Sesquiterpenes
- Diamonipyridimines
- Naphthoquinolones

Nano suspensions in the treatment of malaria



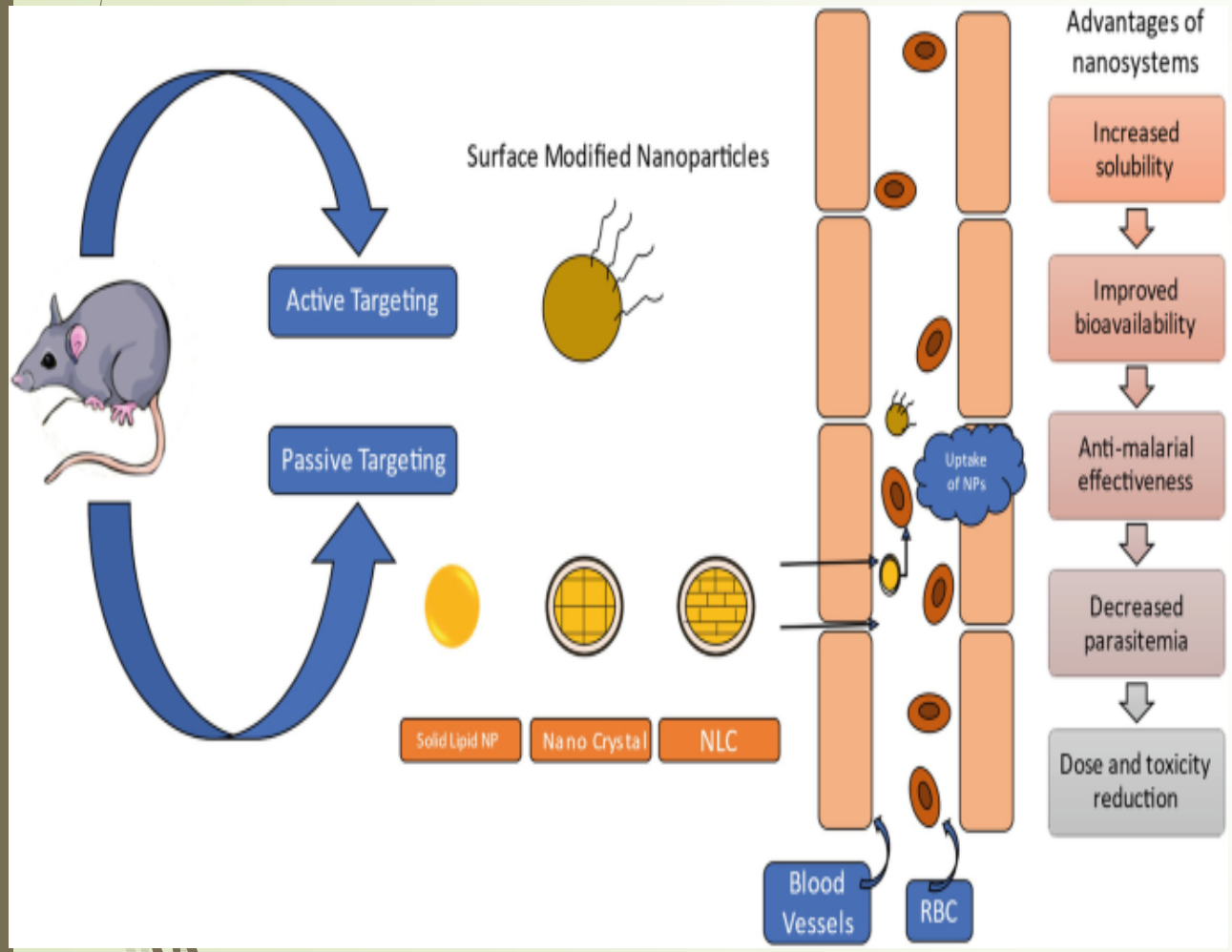
- Patho-biological processes observed in human body after malarial infections
- Destruction of non infected RBC's
- Invasion and destruction of reticulocytes
- Higher fragility of both non infected and infected eruthrocytes
- Infiltration of pulmonary tissues leading to malaria related acute respiratory distress syndrome
- Pregnancy associated malaria
- Splenic hematoma with or without trauma and thrombocytopenia

Nano suspensions in the treatment of malaria



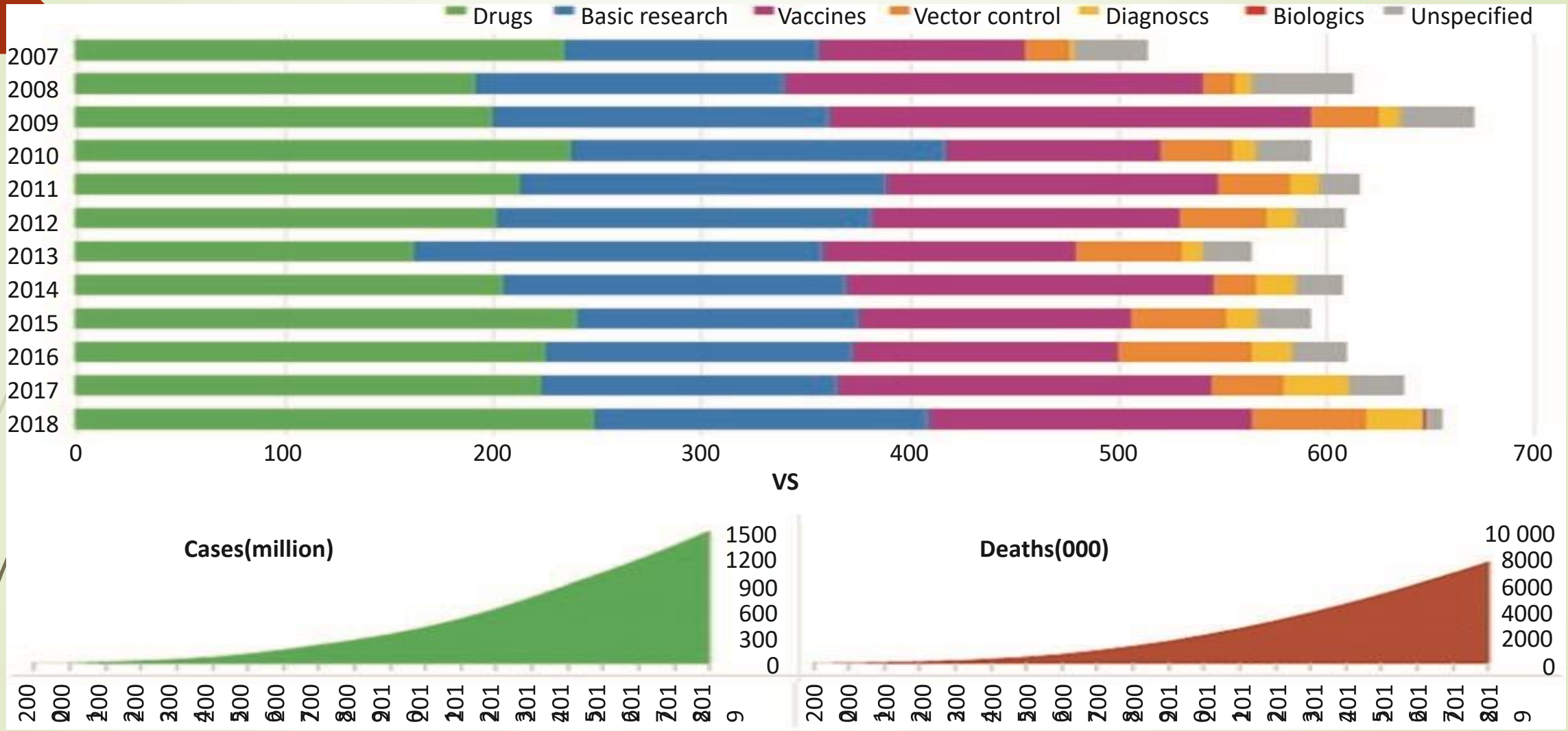
High shear Homogenizer used for nano suspensions manufacturing

Nano suspensions in the treatment of malaria



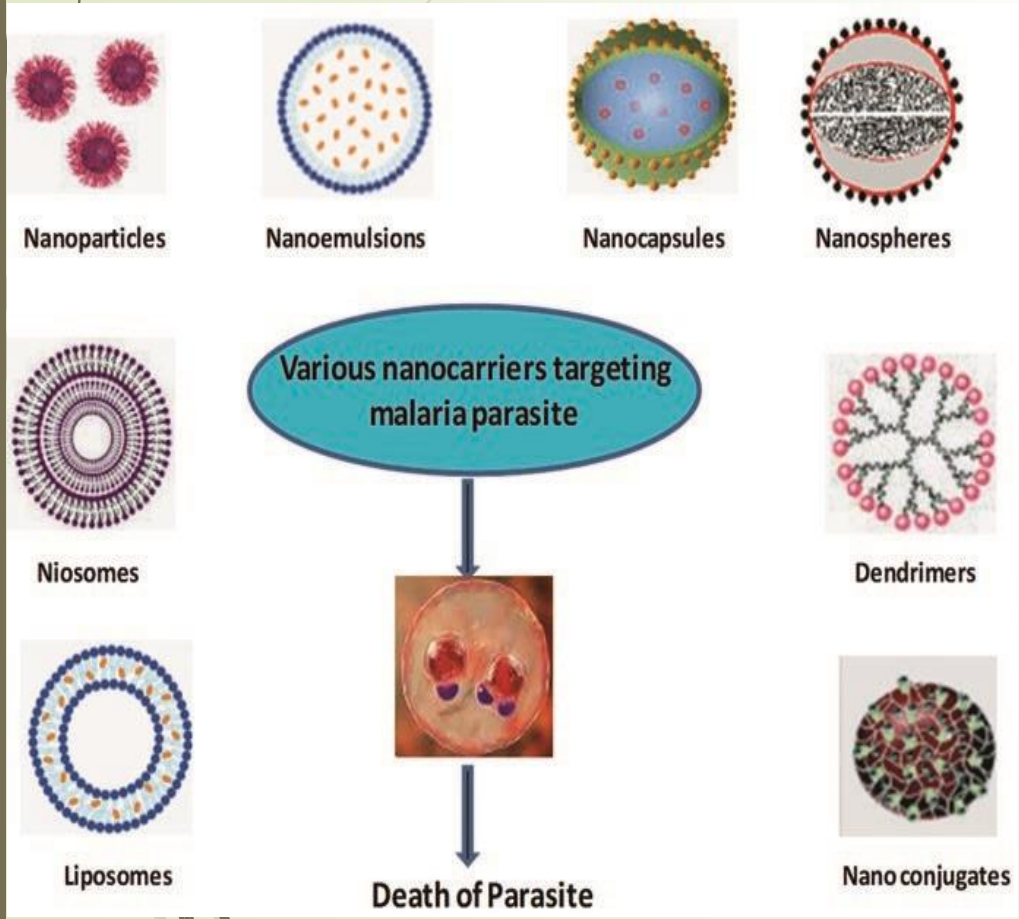
- **Combination of antimalarial tried in nano Suspension drug delivery systems:**
- Artemether and Lumefantrine
- Artesunate and amodiaquine
- Artesunate and mafloquine
- Artesunate and sulfadoxine plus pyrimethamine
- Dyhydroartemisinin and Piperaquine

Niosomes in treatment of malaria



Investment /cases and deaths per year due to malaria

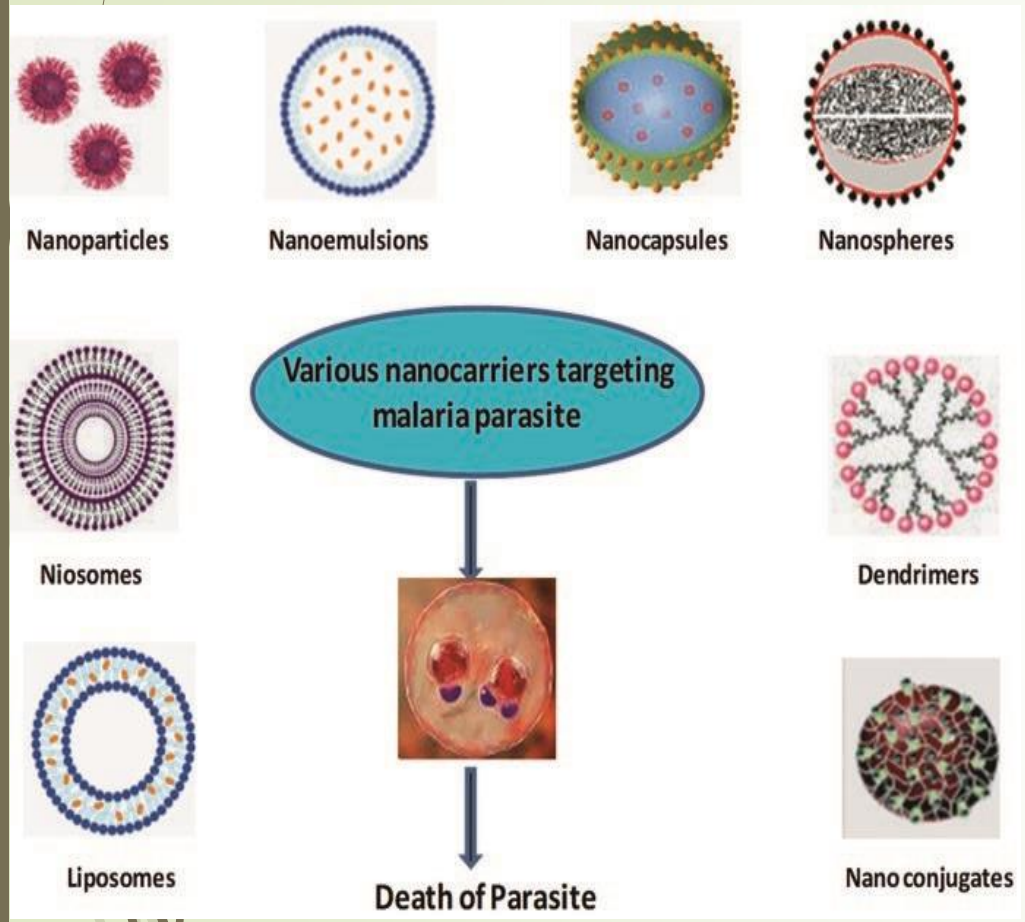
Niosomes in malaria:***Advantages and Disadvantages of Niosomes***



Nano carriers targeting malaria

- Niosomes offer certain advantages as follows [38–42]:
- Niosomes are biodegradable, biocompatible, and non-immunogenic.
- Unacceptable solvents do not use for production.
- No special handling and storage conditions are required as noisome has chemical 183 stability due to its structural composition.
- Various properties, for instance, shape, fluidity, and size of niosomes, are simply 185 controlled by altering their structural components and manufacturing methods. 186 • The high stability exhibited by long shelf life of niosomes permits the delivery of 187 drugs at specific targets in a controlled way.

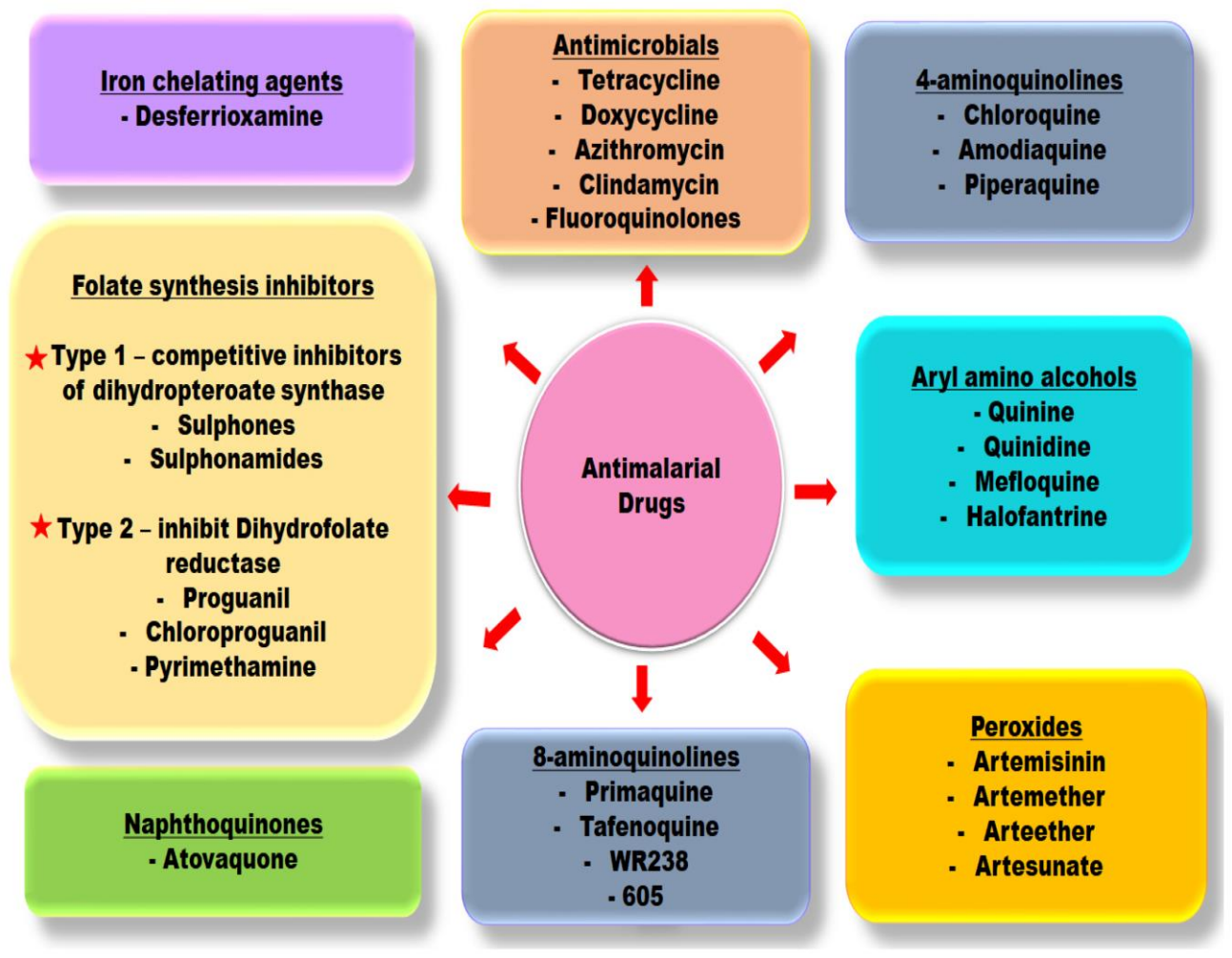
Niosomes in malaria :***Advantages and Disadvantages of Niosomes***



Nano carriers targeting malaria

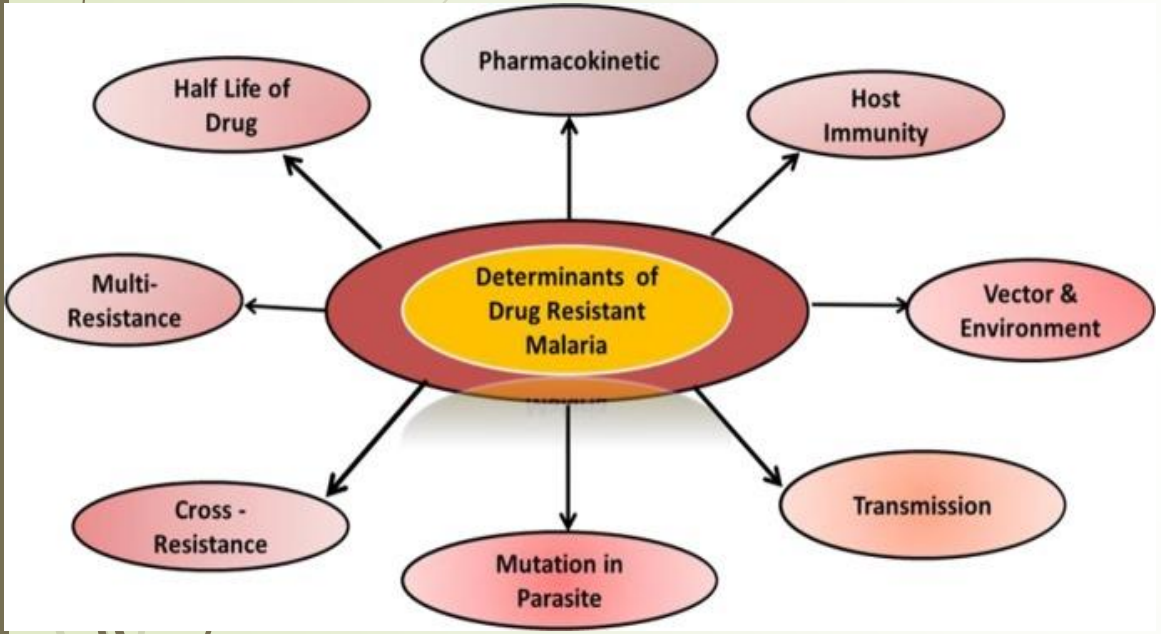
- Niosomes can be easily administered by different routes using different dosage forms.
- It improves the bioavailability of poorly soluble drugs administered orally and 191 increases the permeability of drugs by topical application.
- They are a better alternative compared to oily formulations in terms of patient compliance.
- On the contrary, niosomes show certain stability problem during storage such as "aggregation, fusion, drug leakage, or hydrolysis of encapsulated drugs."

Some antimalarial drugs and combinations sued in Niosomes



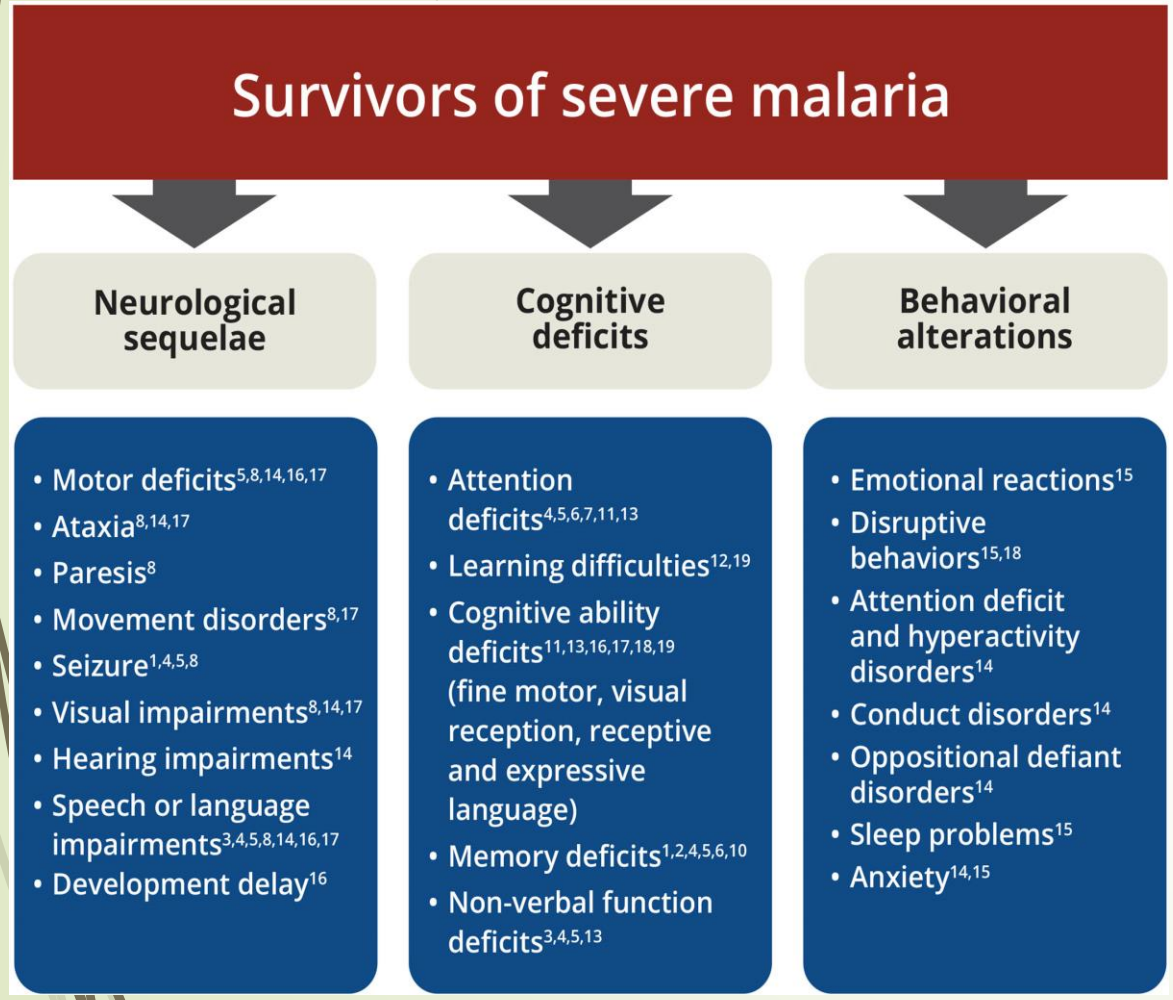
- **Artemether:** Artemether (ART) is a methyl ether derivative of dihydroartemisinin which is considered to be effective in reducing mortality due to severe malaria
- **Artesunate:** Artesunate is a partial synthetic derivative of artemisinin. Artesunate has a short half-life which requires its frequent administration. A lower parasite suppression was found concerning free artesunate.
- **Dihydroartemisinin** : Dihydroartemisinin (DHA) is known to be one of the earliest identified derivatives 278 of artemisinin with substantial antimalarial activity used PLGA, PEG nanoparticles
- **Lumefantrine**: Lumefantrine was previously known as benflumetol, which is an antimalarial drug 313 belonging to the phenanthrene class which is known to be effective against all 314 malarial used Hydroxy propyl methyl cellulose (HPMC polymers) for drug delivery

Challenges with malaria treatment



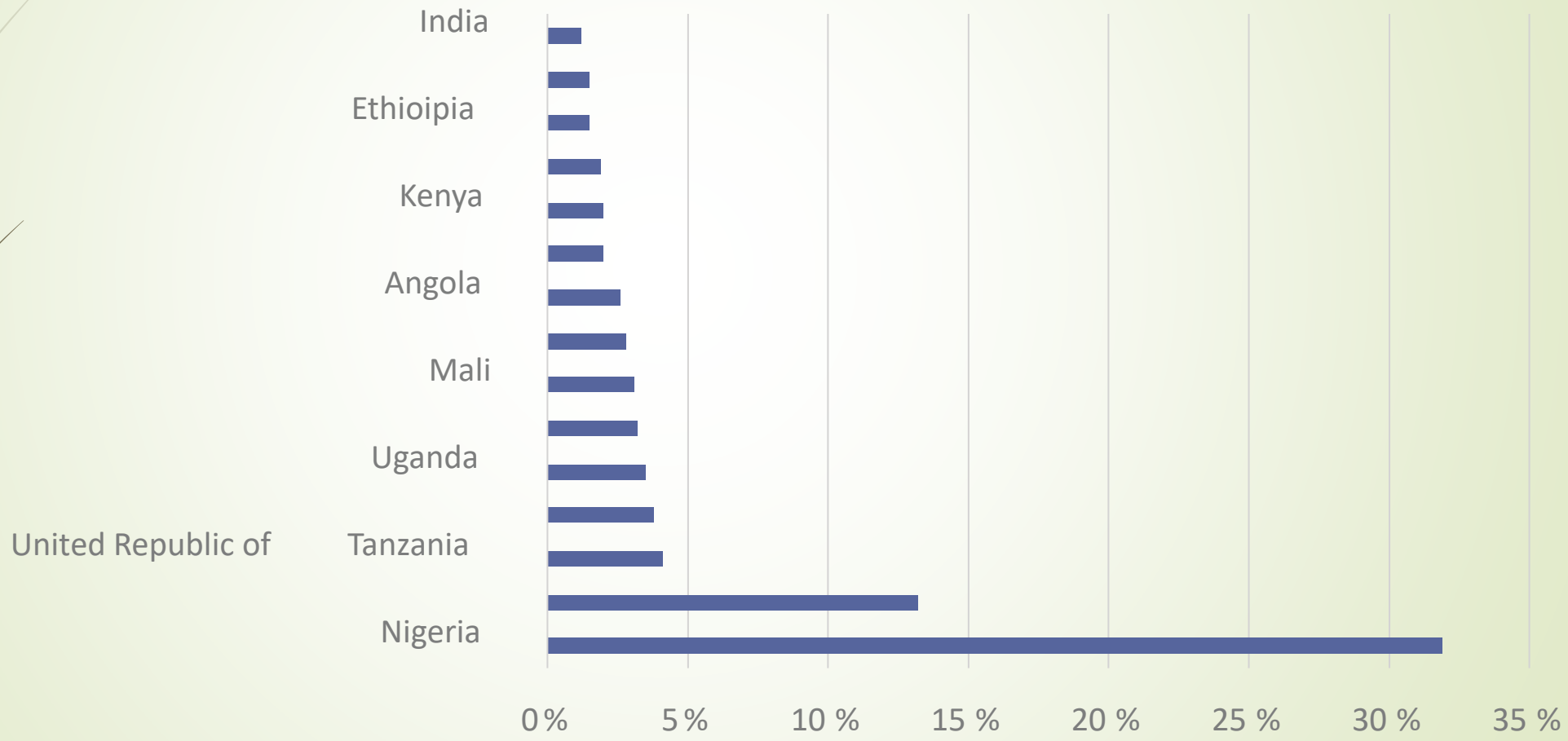
- Over the past six decades, the drug resistance of *Plasmodium falciparum* has become an issue of utmost concern.
- Despite the remarkable progress that has been made in recent years in reducing the mortality rate to about 30% with the scaling-up of vector control, introduction of artemisinin-based combination therapies and other malaria control strategies, the confirmation of artemisinin resistance on the Cambodia–Thailand border threatened all the previous success.
- Antimalarial drug resistance, insecticide resistance, and other mosquitos' survival tactics are the critical challenges towards the goal.
- For decades, antimalarial drug resistance remained the greatest challenge for malaria control and has been documented for almost all antimalarial drugs in current use

Challenges with malaria treatment



- Remarkable failure rates of these combinations have been observed in several African countries where resistance to one drug has been previously encountered, like in the case of artemether-lumefantrine.
- Artemether-lumefantrine remains highly effective in most parts of the world, with the exception of Cambodia. This combination mostly shows failure rates less than 10%.
- However, resistance to most of these combinations will probably lead to a global epidemic outbreak of malaria.

Percentage contribution of malarial global deaths : Who should do the Antimalarial research ?

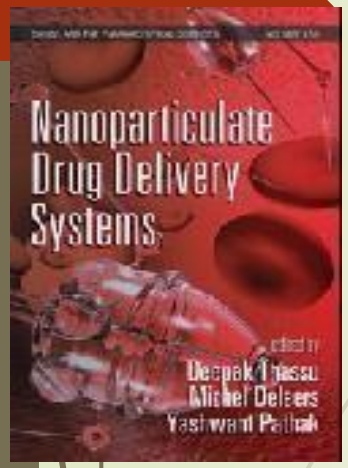


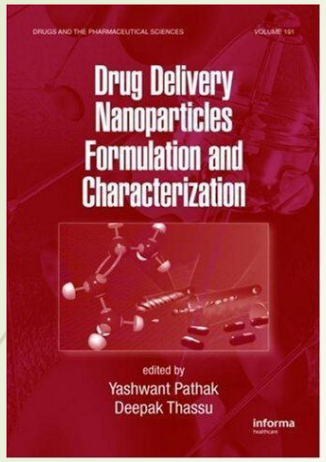
Work with the best - Hope for the best

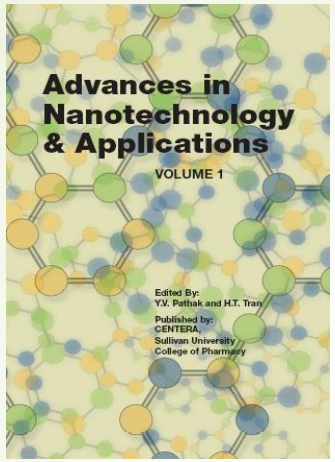
- Currently, the biggest concern all over the globe is to treat patients with safe and effective medications and to avoid the emergence of drug-resistant malaria parasites. However, the emergence of vector resistance to widely used insecticides and parasite resistance to first-line drugs including artemisinin combination therapy has resulted in a rise in malaria incidence in many endemic areas,
- This has called for development of new therapeutic and technology approaches to combat the disease and impede drug resistance. However, more progress and better understanding in terms of scientific research and innovation is needed to develop these novel technologies as tools to reduce the occurrence of malaria.
- New technologies are developed using RNAi (RNA interference) Stem cells , peptides and nanotechnology
- Let us se who wins the race?

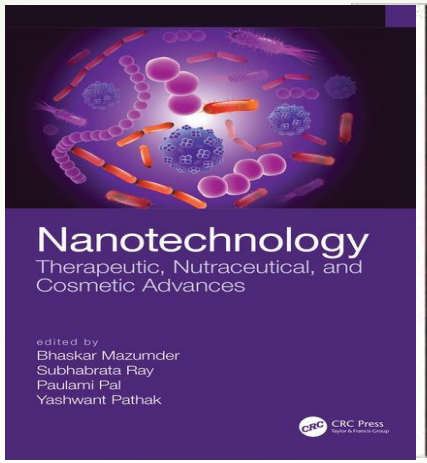
If nothing works this works for sure, age-old wise approach: prevention is better than cure

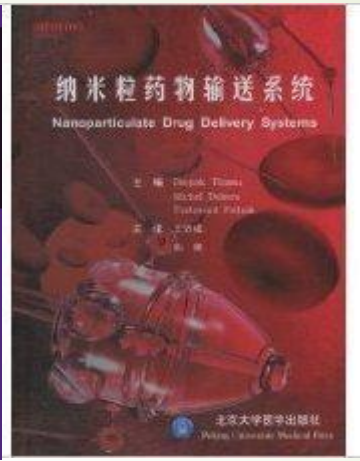
Books in Nano Sciences

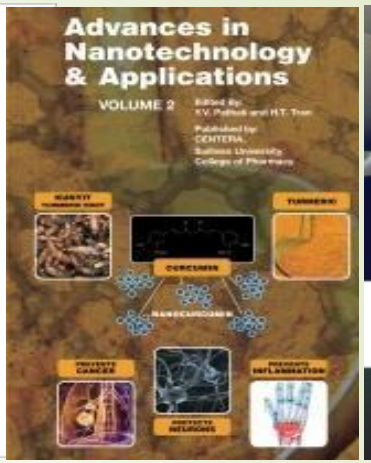


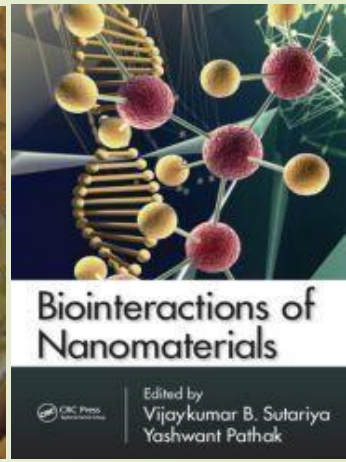


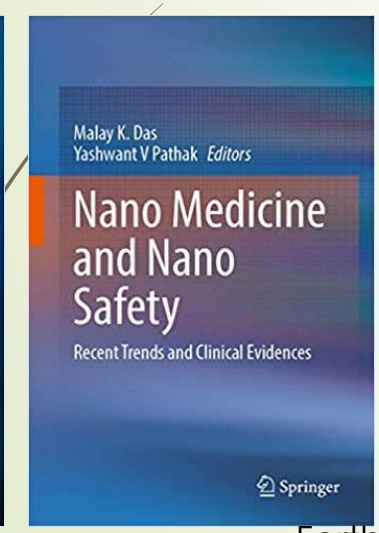


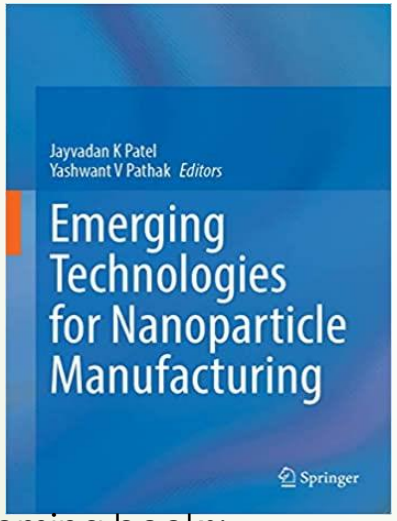


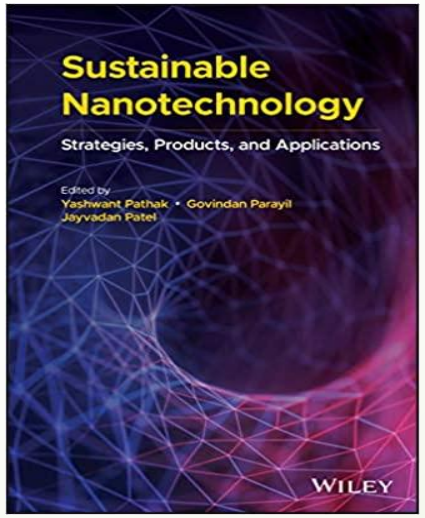


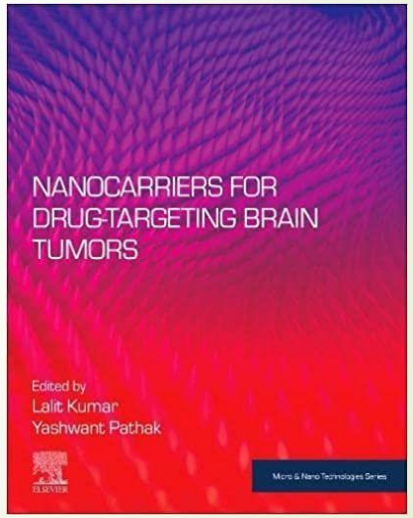


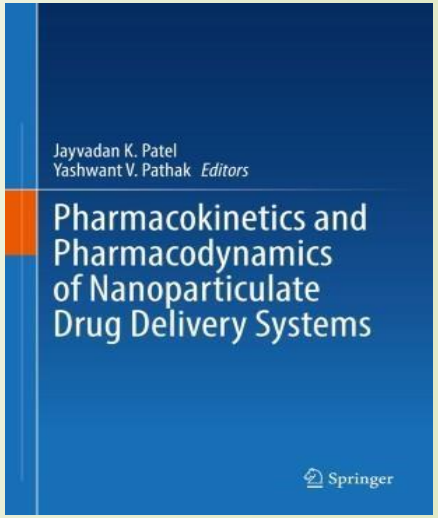








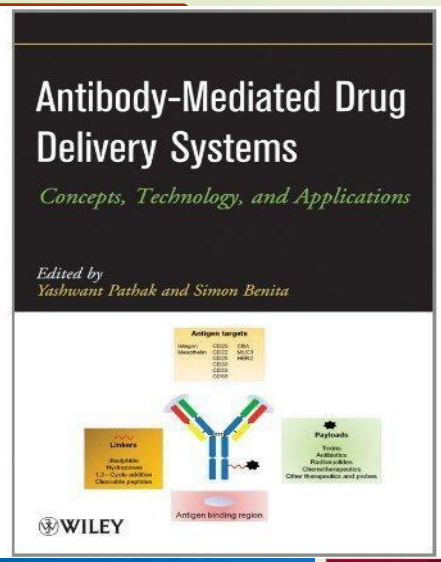


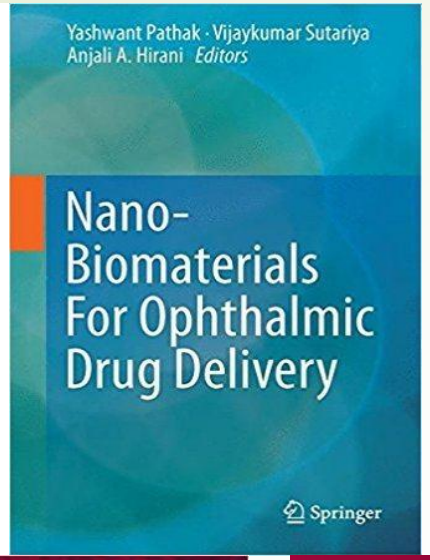


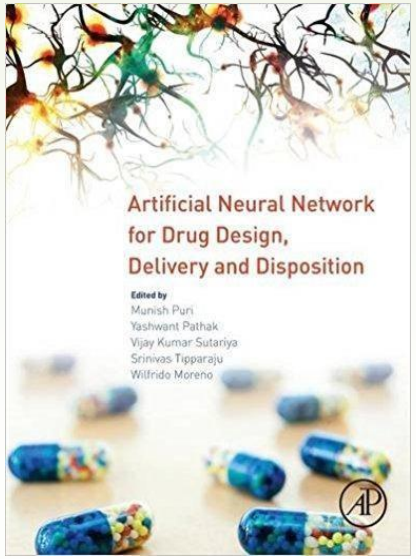
Forthcoming books:

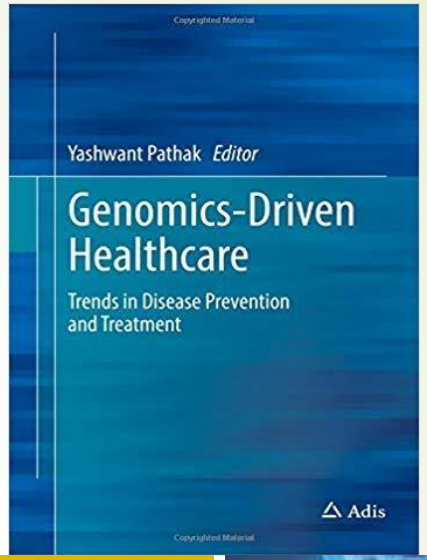
Nano carriers for nasal drug delivery systems (2022)

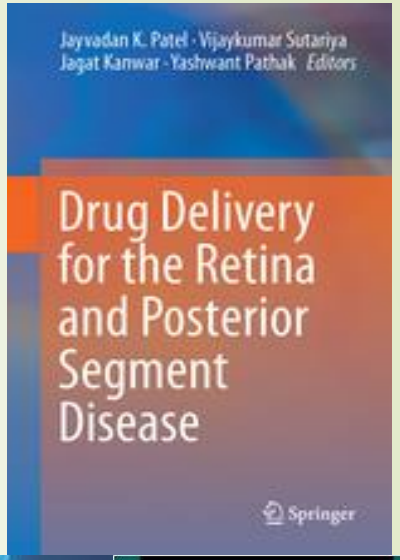
Books in Drug Delivery Systems

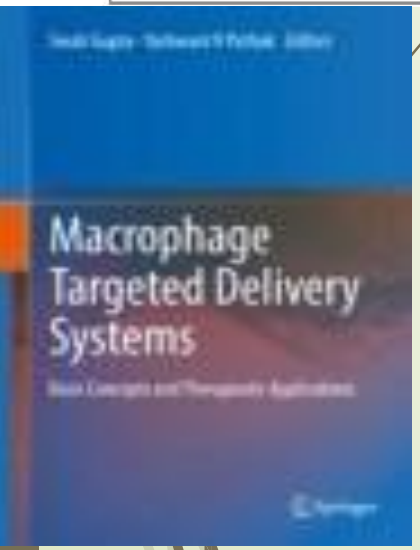


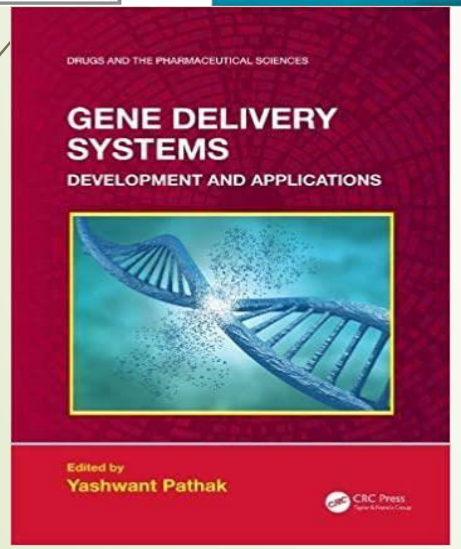


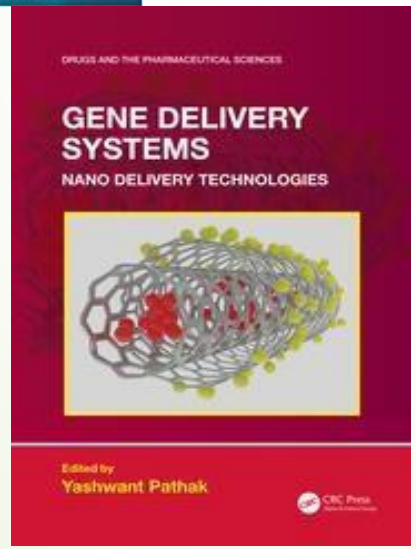


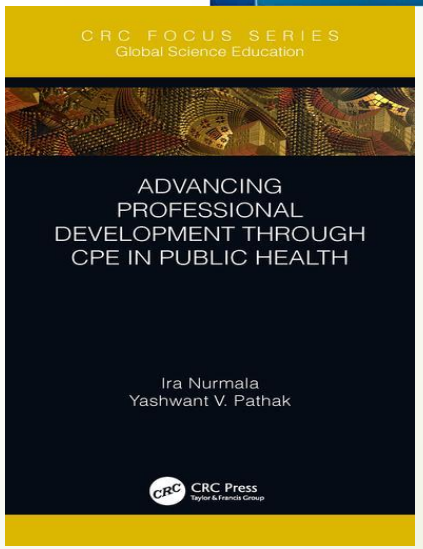


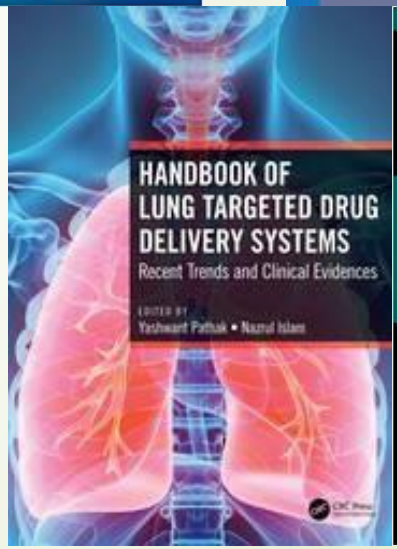


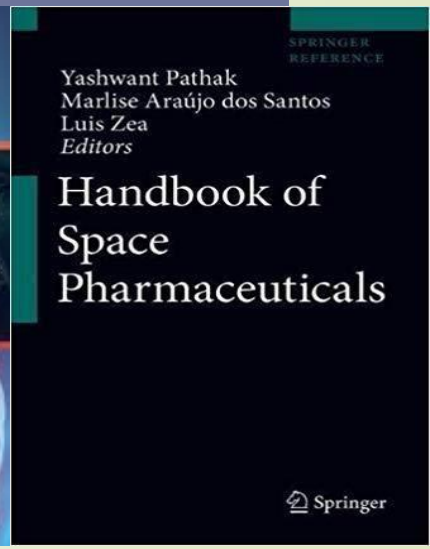




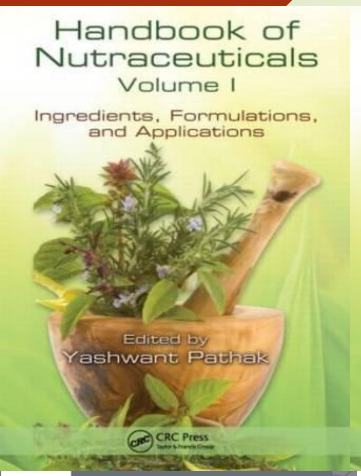


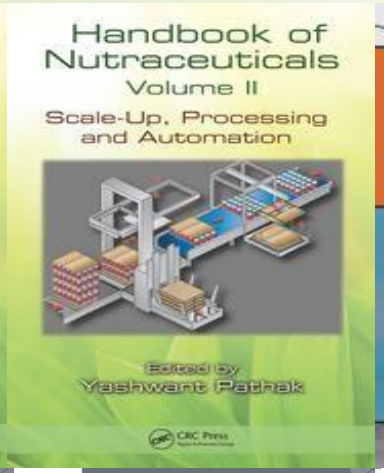


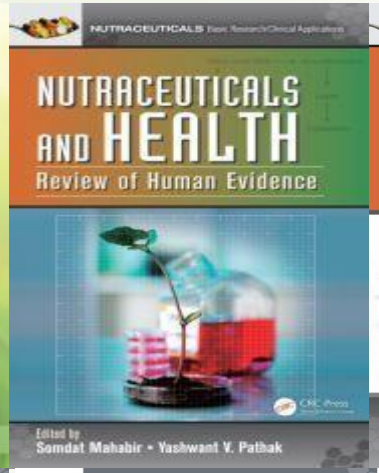


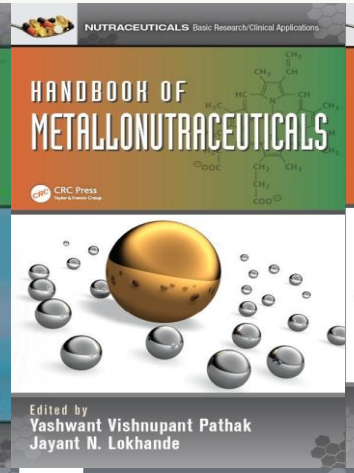


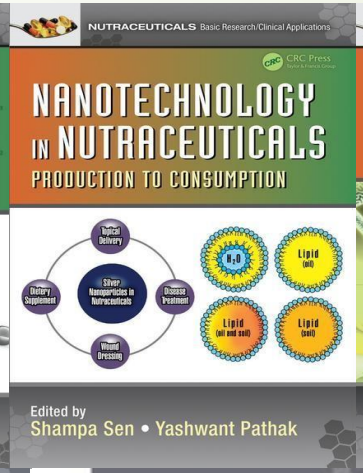
Books in Nutraceuticals

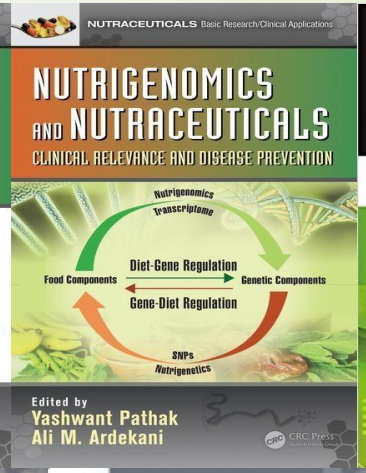


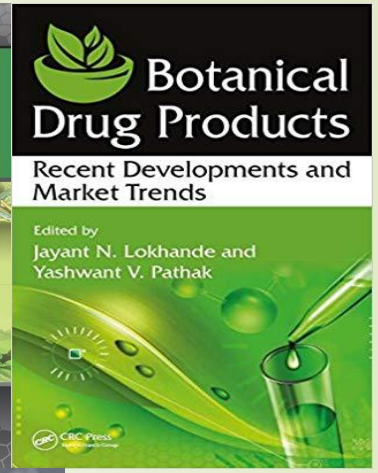


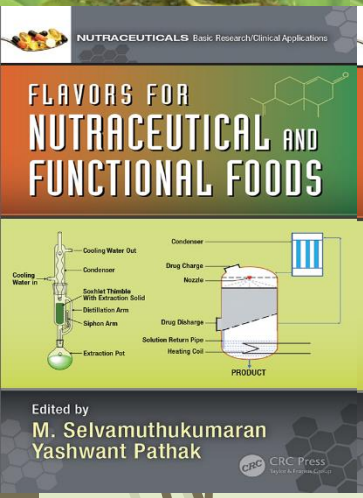


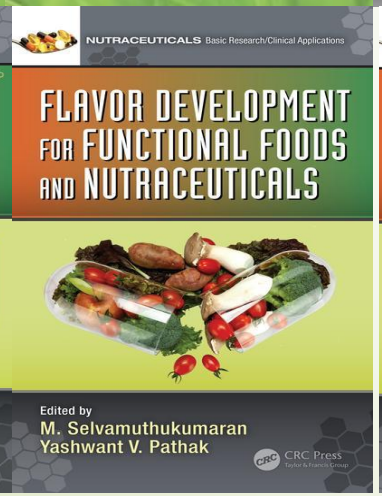


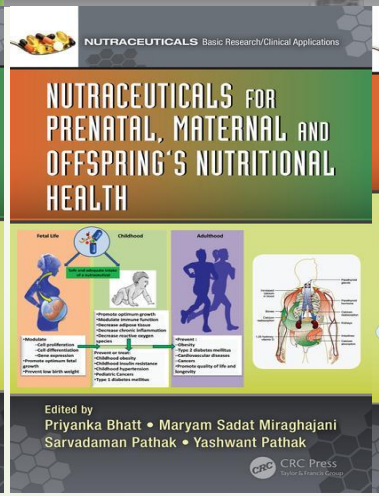


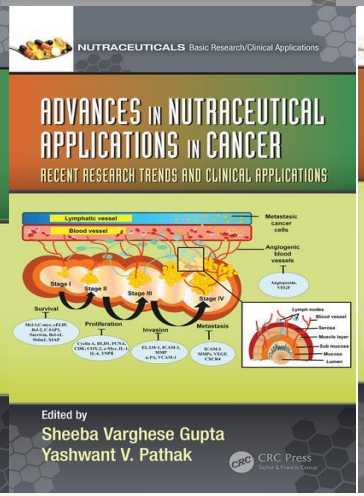


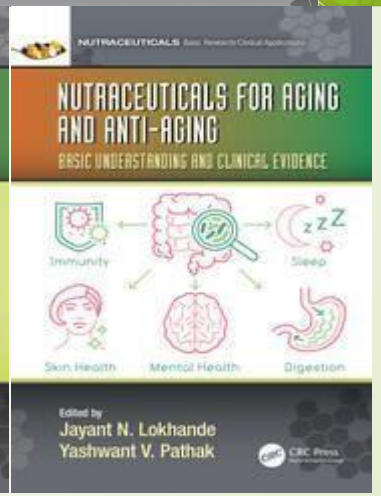












Ma-salama

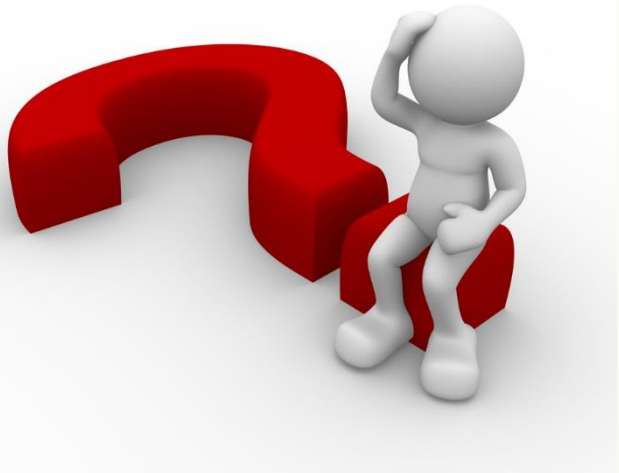
migwe'c (megwitch) Thank You (Native American Language)

Mochas Gracias

Minnetdaram

Obrigado

谢谢



תודה רבה
(*todá rabá*, "thank you very much").

Thanks

Diversity is soul of humanity