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# The Battle Against Malaria

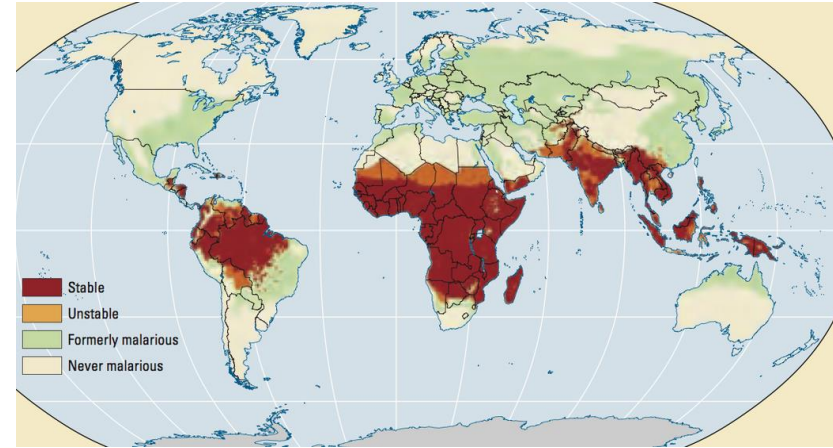
Is a New Superweapon in Sight?

15-09-2022

Dr Chris Williams

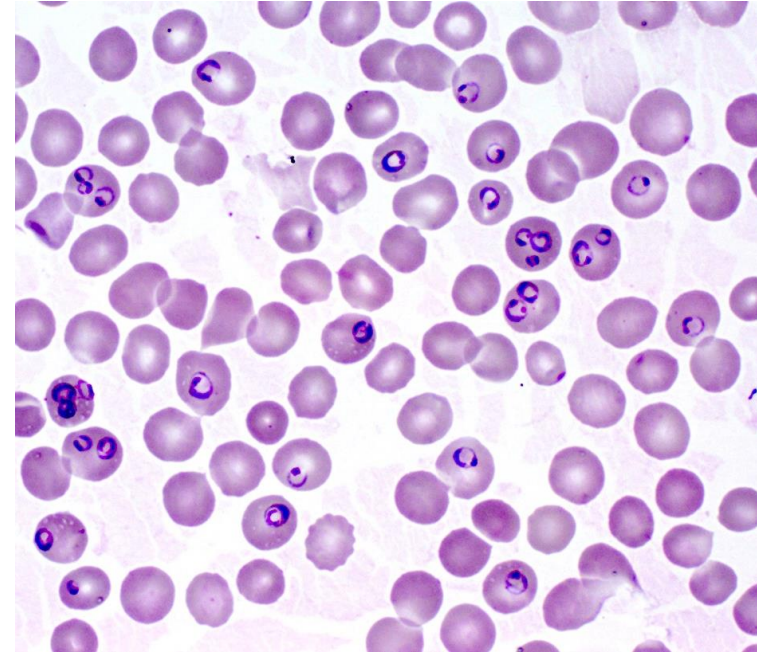
- What is Malaria and why does it matter
- Historical treatments
- Why we need new treatments
- Malaria and vaccines
- The silver bullet

- Malaria is a disease caused by infection with *Plasmodium* parasites
- Approximately 40% of the world's population are at risk of malaria although most cases are in sub-Saharan Africa
- Malaria is estimated to kill just under half a million people each year, the majority of which are infants
- That's approximately 1 child every 2 minutes of every hour, every day

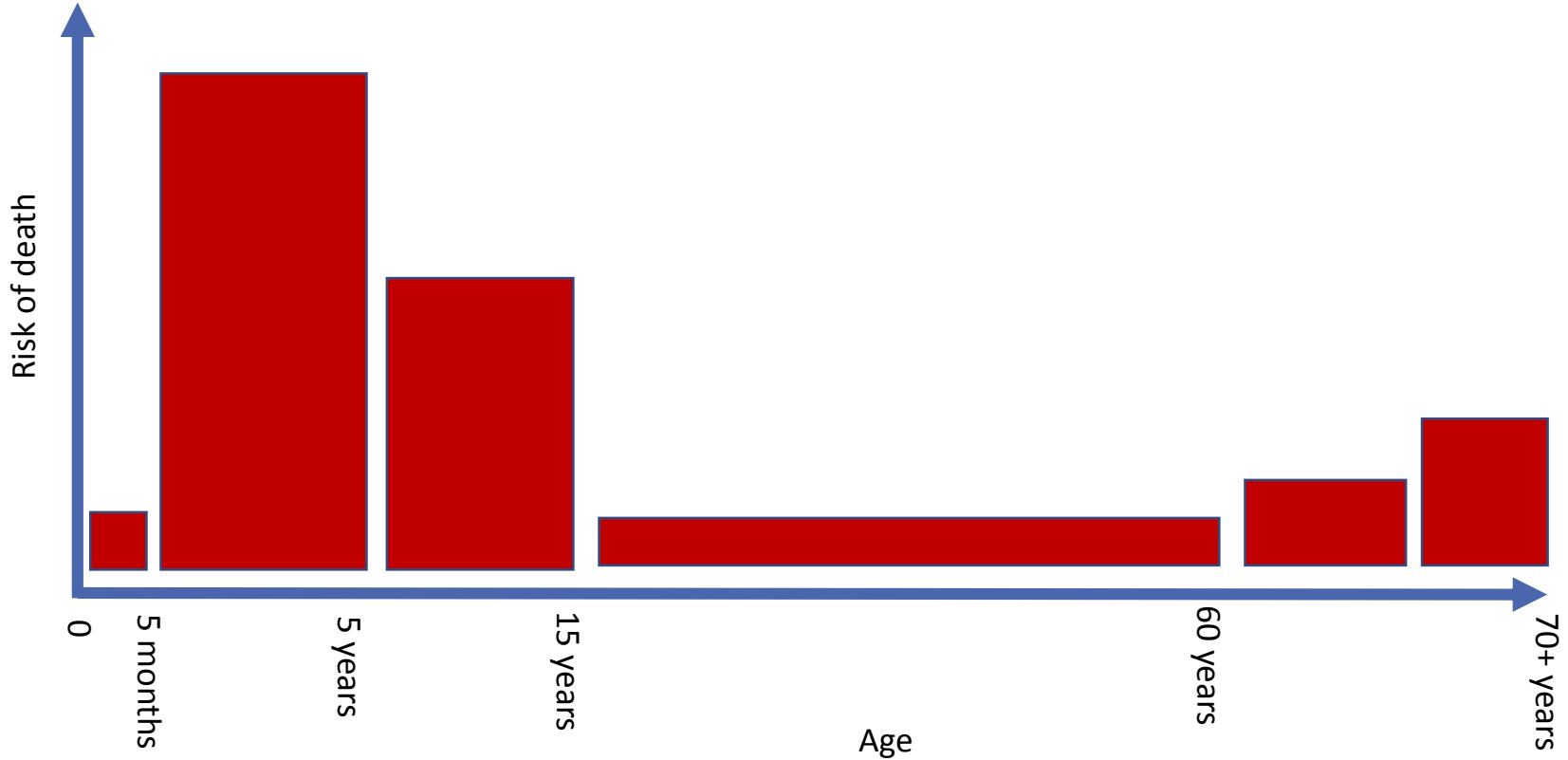


# So Malaria Isn't Caused By a Virus?

- Many diseases are caused by bacteria or viruses but some are caused by parasites.
- Parasites range from tape worms to single cell protozoan (like the malaria parasite).
- These grow much slower than viruses and bacteria but are much bigger and much more sophisticated!
- Humans have between 20,000-25,000 genes, HIV has 15 and malaria parasites (Plasmodium) has 5500!



# A Disease Of The Young?

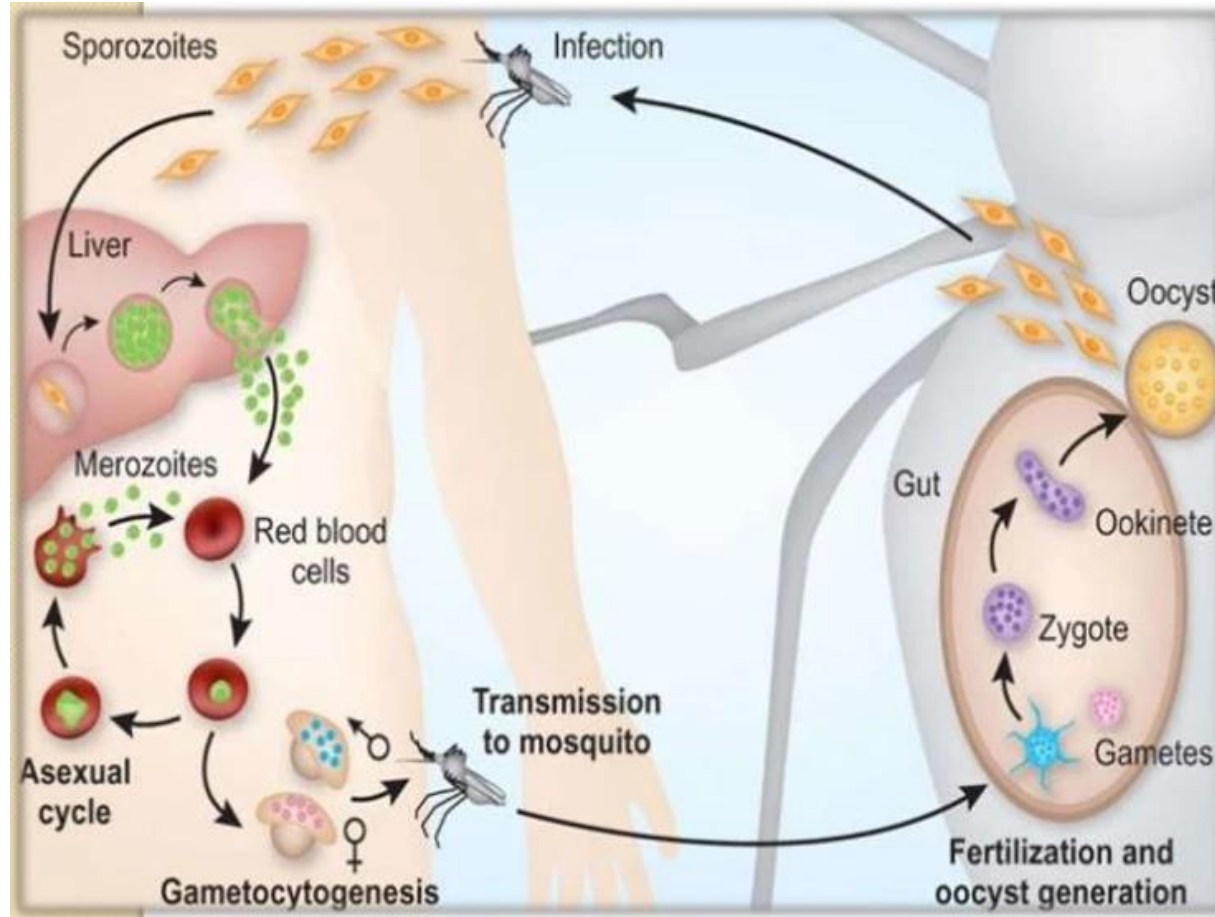


- The majority of deaths are between 5 months and 5 years

- The parasite that causes malaria is transmitted by female Anopheles mosquitoes
- Anopheles mosquitoes are found in the UK, but the parasite needs a temperature of  $\sim 27^{\circ}\text{C}$  for 10 days to grow inside the mosquito
- Malaria was common in the UK in the 17<sup>th</sup> century and could be again!

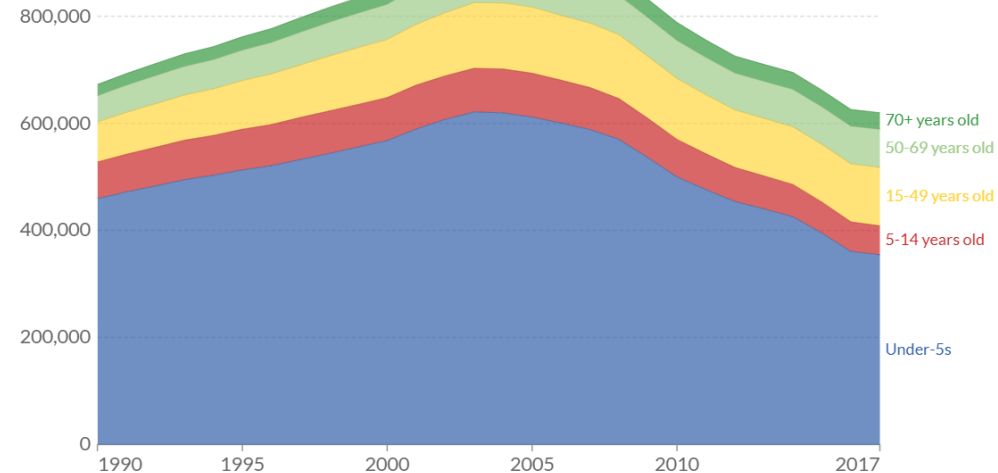


# Life Cycle Of The Parasite



- The malaria parasite is now resistant to a range of anti-malarials
- The number of cases of untreatable malaria is raising
- The mosquito carrier has become resistant to many insecticides
- There is currently no effective vaccine

Deaths from malaria, by age, World, 1990 to 2017



Source: IHME, Global Burden of Disease (GBD)

OurWorldInData.org/malaria/ • C



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- The average drug takes 10 yrs to develop and costs ~ \$1billion
- There is limited chance of making any profit with an anti-malarial
- Despite this, many types of anti-malaria have been developed but resistance now exists to all of them

Antimalarial Drug	Mechanism of Action	Site of Action	Mechanism of Resistance
Antifolates ((pyrimethamine (PYR) and cycloguanil (CYC))	Inhibition of dihydrofolate reductase (DHFR)	Cytosol	Mutations in dihydrofolate reductase (DHFR)
Antifolates (sulfadoxine (SDX))	Inhibition dihydropteroate synthetase (DHPS)	Cytosol	Dihydropteroate synthetase (DHPS)
Naphthoquinones (Atovaquone (ATQ))	Inhibits mitochondrial electron transport	Mitochondria	A single point mutation in the cytochrome b subunit (CYTb) of the bc1 complex
Antibiotics (Clindamycin (CLD) and Doxycycline (DOX))	Inhibit protein translation inside the apicoplast	Inside the apicoplast	A point mutation in the apicoplast encoded 23S rRNA (CLD)
Artemisinin (ART)	Alkylation of proteins and lipids	ER, vesicular structures	Mutation in K13
4- aminoquinolines (CQ, AQ, PPQ, Mannich base pyronaridine (PND))	They bind reactive heme and interfere with its detoxification through incorporation into chemically inert hemozoin.	Digestive vacuole	Point mutations in the transporters PfCRT and PfMDR1, increased expression of the hemoglobins plasmepsin 2 and 3 (PM2/PM3, in the digestive vacuole), and might in some instances involve mutant PfCRT

- There are many problems of chemotherapy for treatments in developing countries.
- Access to the drugs can be disrupted by conflict, poverty, corruption etc
- Families that cannot afford enough drugs for multiple children will often drug tablets in half meaning neither child gets a sufficient dose.
- Local shops may sell counterfeit drugs or even split courses

- DDT is a powerful insecticide, first used in WW2 to reduce the impact of malaria
- In the 1950s and 60s the WHO relied heavily on DDT to eliminate malaria
- DDT resistance, reported in multiple areas in 1956, was one of the reasons the WHO strategy failed.
- DDT then built up in the food chain killing many large predators such as eagles.
- It also entered the human food chain to cause birth defects

- DDT was banned for agricultural use in the 1970s
- Indoor residual spraying (IRS) is still used effectively where there is limited resistance
- But ~80% of humans within a given area must be sprayed to have a significant effect on malaria case numbers



- Anopheles mosquitoes feed mostly at night so bed nets can stop transmission.
- But mosquitoes can bite through the net if any body parts are touching the net
- Insecticide treated bed nets are more effective, especially as mosquitoes will rest after a feed
- But can be toxic if babies/children put them in their mouths



- Mosquitoes can breed in any standing water
- Introducing larvae predators can help in some sites
- Some other sites can be removed but never all!

Rice paddies



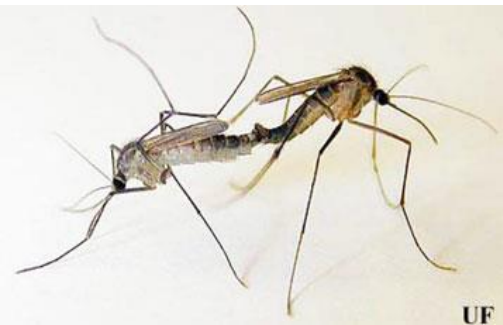
Irrigation channels



Water containers



Drainage ditches



- Mosquitoes only mate once so sterile males be made in a lab and released into the wild.
- This method works on enclosed areas like Islands but less so in open areas

- What is Malaria and why does it matter



- Historical treatments



- Why we need new treatments

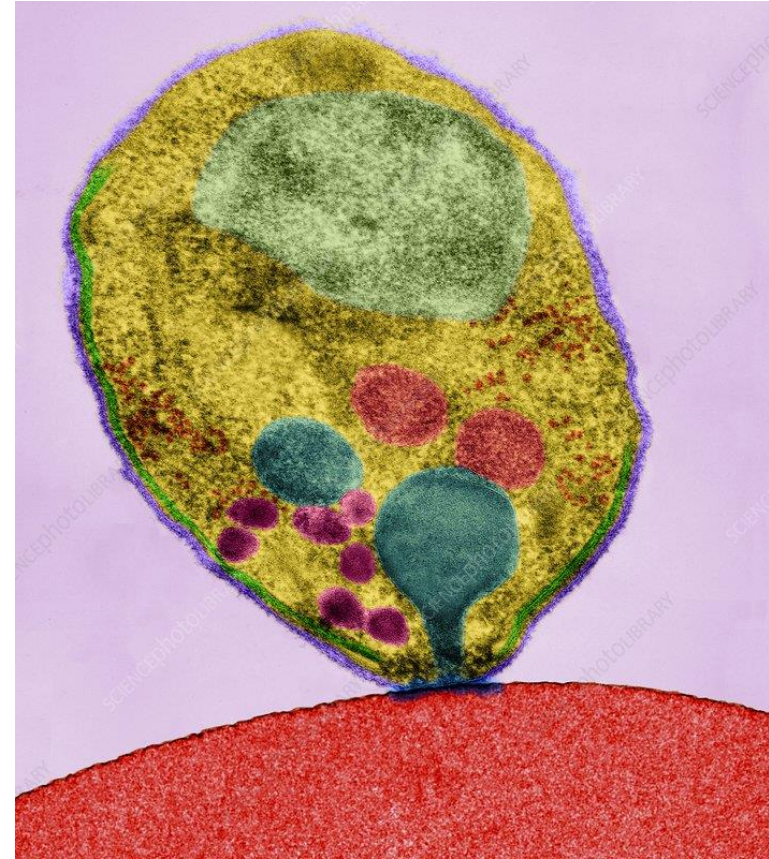


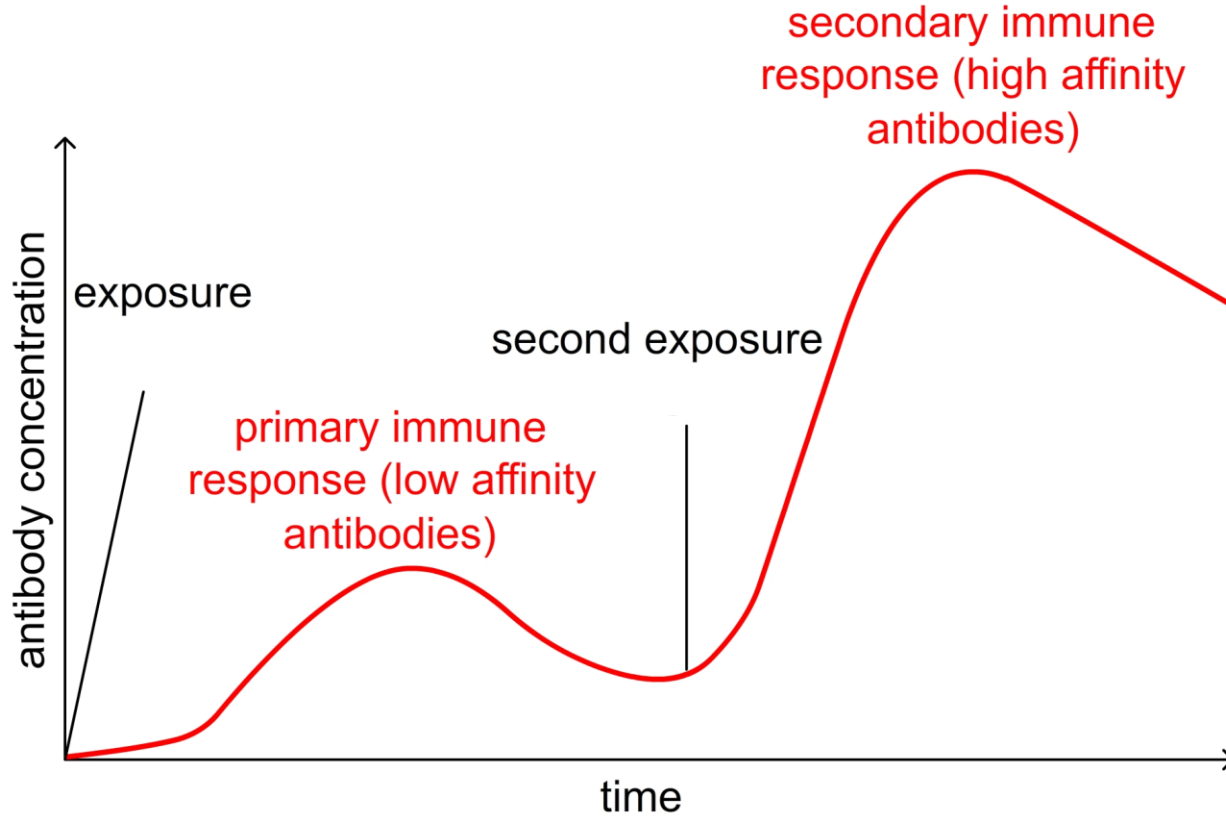
- Malaria and vaccines

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- We have this sophisticated immune system yet a single cell parasite can still kill us?
- But some people can recover from malaria without help?
- We have been locked in this arms race for over half a million years!





- So the immune system can develop protection against malaria
- With most diseases immune memory develops after 1 or 2 infections and can last decades
- With malaria, it takes 100s of infections and may only last 1 or 2 years without new infections (boosters)
- Strangely, this problem is unique to humans

- At any time there are more than 100 groups working world wide trying to develop a new malaria vaccine!
- This has been the case for decades!
- Last year first malaria vaccine was approved!
- The only problem, it's pants!

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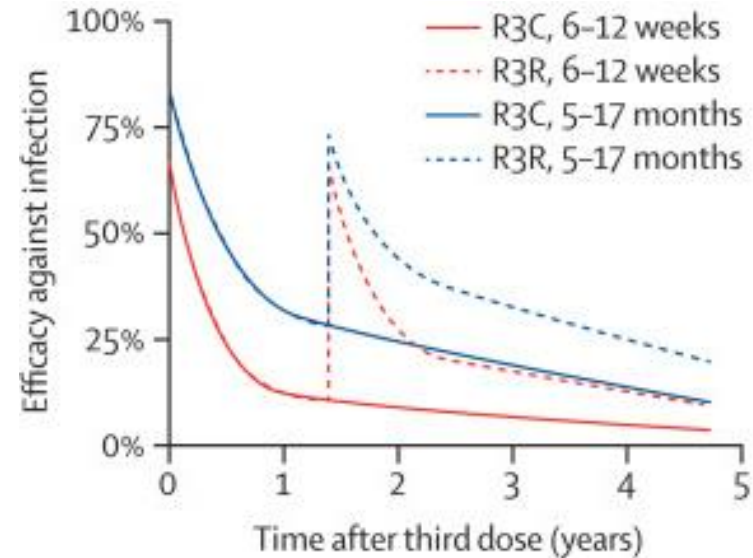
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### Historic go-ahead for malaria vaccine to protect African children

By James Gallagher  
Health and science correspondent

🕒 6 October 2021

- Developed by GSK, the vaccine targets the parasite on it's way and when it gets to the liver
- It gives no protection against the blood stage!
- It has been in development since 1987!
- It was approved because it is safe and we have nothing better.



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- Malaria and vaccines



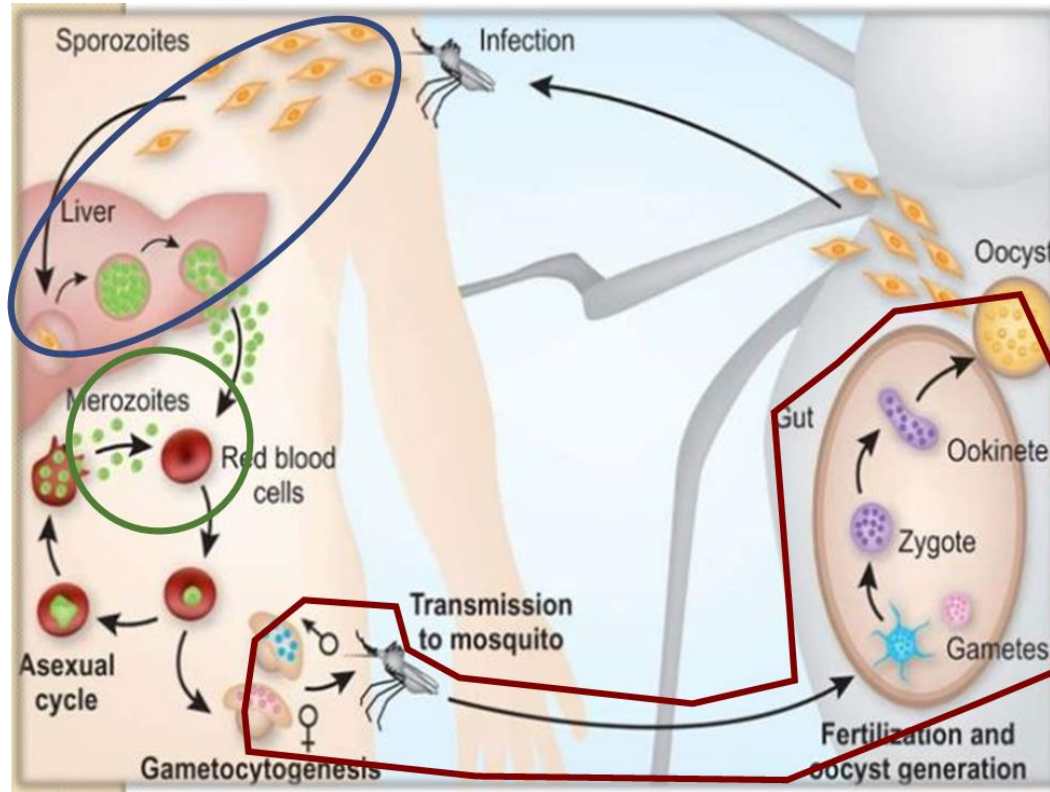
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- A research institute that is focused on the development and testing of new vaccines
- Part of Oxford University, on the Old Road Campus (next to the Churchill hospital)
- Has groups working on malaria, TB, HIV and of course covid-19



+ Stopping the parasite before/at the liver will prevent any symptoms  
 - If a single parasite escapes out of the liver it is free to multiply unchecked

+ Stopping the parasite where it causes disease  
 - Window of opportunity is a few minutes every 2 days  
 - This is where the parasite is best adapted to avoiding effective attack



+ Stops mosquitos getting infected and so stops transmission  
 + The parasite is not normally attacked by the immune system here, so has not evolved to protect itself here  
 - Does not give any direct protection to the individual vaccinated



# A Combination Vaccine

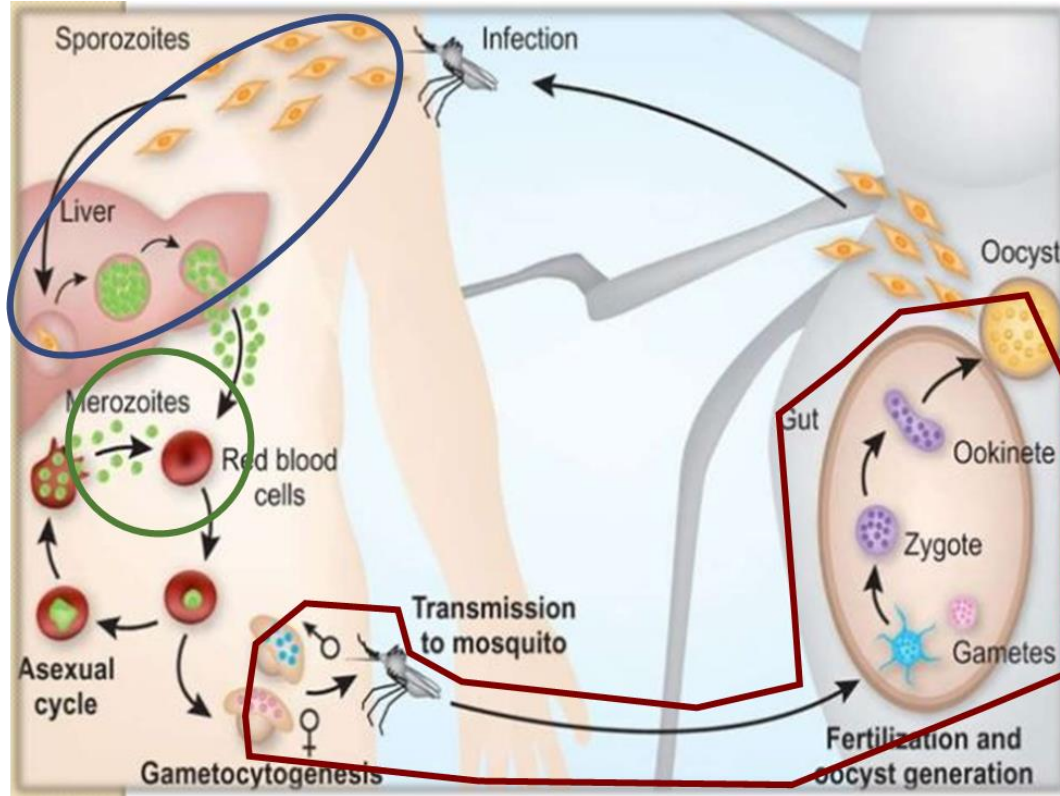
## Greater Than The Sum of Its Parts



Group led by Prof Adrian Hill



Group led by Prof Simon Draper



Group led by Prof Sumi Biswas

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### New malaria vaccine is world-changing, say scientists

By James Gallagher  
Health and science correspondent

