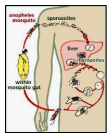
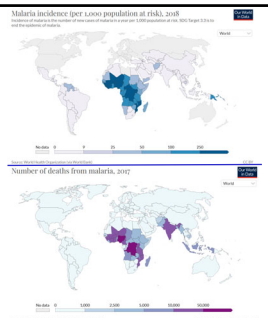
## Malaria: old and new approaches toward control and elimination

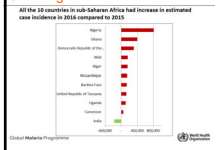



Phil Rosenthal
UCSF
March 16, 2023




## Control vs. elimination

Challenges with control in Africa



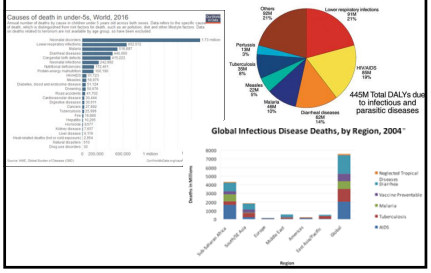

Est. 3.5 million more cases in 2017 compared to 2016

Progress toward elimination:
Of 87 endemic countries:
- 47 with <10,000 cases
- 24 with < 100 cases

Countries recently declared malaria free:
- Sri Lanka 2016
- Kyrgystan 2016
- Uzbekistan 2018
- Paraguay 2018
- Argentina 2019
- Algeria 2019
- El Salvador 2021
- China 2021

## Global importance of malaria

A leading cause of morbidity and mortality in children




## Malaria: Control vs. Elimination

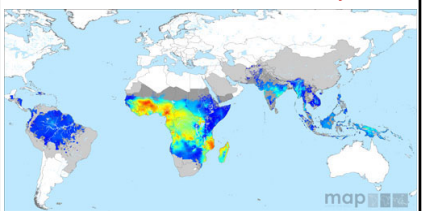
- Control – goal is decreased morbidity and mortality
- Elimination
  - Interruption of local transmission
  - For a country to be certified malaria-free:
    - No cases over the last 3 years
    - Demonstrated capacity to prevent re-establishment of transmission
- Eradication – the whole world

## Updates from 2022 World Malaria Report

- Malaria cases:
  - 2015: 230 million
  - 2020: 245 million
  - 2021: 247 million
  - Case incidence (cases/1000/yr)
    - 2000: 82 2015: 59
    - 2019: 57 2021: 59
- Malaria deaths:
  - 2000: 897,000 2015: 577,000
  - 2019: 568,000 2021: 619,000
    (68% ↑ 2020 due to COVID-19)
  - % children < 5 yrs
    - 2000: 87%
    - 2015-present: 76%
  - Mortality rate (deaths/100,000)
    - 2000: 30 2015: 15
    - 2019: 14 2021: 15

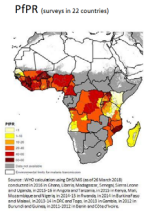

Important impact of COVID-19 on malaria control (63,000 excess deaths)

## Malaria transmission intensity



Relative transmission intensity from low (blue) to high (red)

## Malaria: Control vs. Elimination



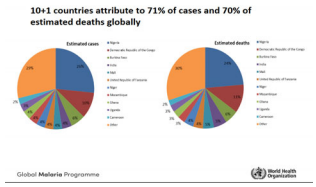

Many countries are approaching elimination.

Many countries have continued very high prevalence, especially in Africa.

## The current WHO strategy

- WHO Global Technical Strategy for Malaria 2016-2030 (adopted May, 2015) targets for 2030:
  - Reducing malaria case incidence by at least 90%.
  - Reducing malaria mortality rates by at least 90%.
  - Eliminating malaria in at least 35 countries.
  - Preventing resurgence in malaria-free countries.
- Three key pillars:
  - Ensuring universal access to malaria prevention, diagnosis, and treatment.
  - Accelerating efforts towards elimination.
  - Transforming malaria surveillance into a core intervention.

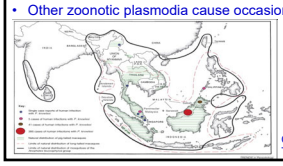
## The latest WHO program
## High burden to high impact
(Formerly "10 +1")




2021 WMR: 29 countries accounted for 95% of malaria cases.
Highest: Nigeria (27%), DRC (12%), Uganda (5%), Mozambique (4%)

## *P. knowlesi*: the fifth human malaria parasite (a zoonotic parasite)

- Parasite of macaque monkeys; resembles *P. malariae*
- Re-evaluation cases using molecular methods
  - Most common cause of malaria in Malaysian Borneo and nearby areas
  - Range limited by range of *A. leucosphyrus* group mosquitoes
- Doubling time 24h
- Can cause severe disease and deaths
- Other zoonotic plasmodia cause occasional human disease



Cox-Singh, et al., CID, 2008; Trends Parasitol, 2008

## Malaria RDTs

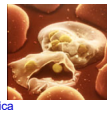
- BinaxNOW malaria test FDA approved 2007
- Detects:
  - *P. falciparum*-specific antigen (HRP2)
  - Antigen all human plasmodia (aldolase)
- Approved for hospital and commercial labs
- How good is the test?

| | *P. falciparum* | *P. vivax* |
|---|---|---|
| Sensitivity | 99.7% | 93.5% |
| Specificity | 94.2% | 99.8% |

(tested at parasite density > 5,000/µl)

- Many tests available worldwide
  - HRP2 – most sensitive, but limitations:
    - Can remain positive for a few weeks after clearance of parasites
    - Some parasites do not express HRP2 (S. America, Horn of Africa)
    - Doesn't recognize non-falciparum infections
  - LDH
  - Aldolase

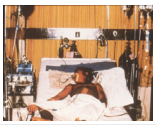
## Key distinction in malaria:
## *P. falciparum* vs. other species



- *P. falciparum* (>95% all cases)
  - Most common and widely distributed parasite
  - Nearly all malaria in sub-Saharan Africa
  - High risk of progression to severe disease
  - Major problems with drug resistance
- *P. vivax*
  - About as common as *P. falciparum* outside Africa
    - Proportion total cases down to ~2% (~4.5 million cases)
  - Hypnozoites
  - Occasionally causes severe disease
  - Increasing drug resistance
- *P. ovale*- uncommon; hypnozoites
- *P. malariae*- uncommon; can be chronic
- *P. knowlesi*- zoonosis; geographically constrained

## Malaria
## Clinical presentation

- Febrile paroxysm
- Respiratory and GI symptoms common
- Uncommon findings: rash, lymphadenopathy
- Fever pattern usually not regular
- Severe disease:
  - falciparum malaria

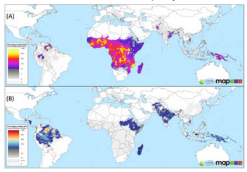


## Malaria control

- Prompt effective therapy
- Other uses of drugs
  - Chemoprevention
    - Chemoprophylaxis
    - Intermittent preventive therapy (IPT)
- Control of mosquito vectors
  - Personal protection (ITNs)
  - Indoor residual spraying (IRS)
- Malaria vaccine

## *P. vivax*

- Uncommon in Africa due to lack of Duffy Ag
- Severe vivax more common than previously appreciated
  - Rural hospital in Papua, Indonesia 2004-07
    - Severe disease about equally common Pf vs. Pv



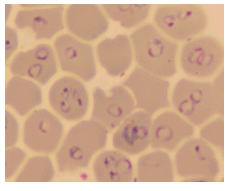

*P. falciparum*

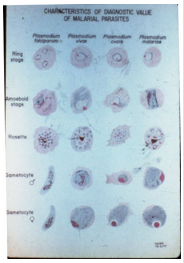
*P. vivax*

Incidence of *P. falciparum* and *P. vivax* malaria in 2017 (cases/1000/yr)

Price, et al. PLoS Med 2008,5:e128
Price, et al., Trends Parasitol, 2020, 36:560

## Diagnosis of malaria- microscopy



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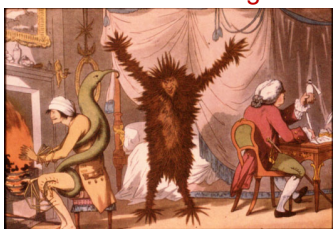
## Antimalarial drugs



Fever and Ague, 1798

## Major antimalarial drug indications

- Treatment of falciparum malaria:
  - ACTs
  - Malarone (atovaquone/proguanil)
- Treatment of other species: chloroquine
  - Vivax and ovale: Also primaquine or tafenoquine
- Chemoprevention:
  - Pregnancy: Sulfadoxine/Pyrimethamine (SP)
  - SMC: SP + amodiaquine
  - Travelers: Malarone or Doxycycline

## Artemisinin-based combination therapy (ACT)

- Short acting artemisinin plus long-acting partner drug
- Now the standard treatment for falciparum malaria in nearly all countries
- Most commonly used regimens
  - Artemether-lumefantrine (Coartem, Riamet)
  - Artesunate-amodiaquine (ASAQ, Coarsucam)
  - Dihydroartemisinin-piperaquine (Artekin, Duocotecxin)
  - Artesunate-mefloquine
  - Artesunate-pyronaridine
  - Artesunate-SP (primarily in India)

## Quinine: the first antimicrobial drug

Cure of the Countess of Chinchon

Torti, 1709

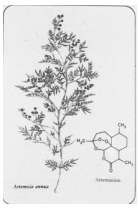
Cinchona trees



Pelletier and Caventou
Isolation of quinine- 1820

## Artemisinins

- Extracted from *Artemisia annua*
- Used as herbal remedy for fevers in China for thousands of years (Qinghao)
- Active ingredient purified 1972 (Qinghaosu)
- Artemisinin and derivatives extensively tested in China beginning in late 1970s
- Used widely to treat malaria by 1980s in China, 1990s in other Asian countries, 200s in Africa



## Artemisinins for the treatment of severe malaria

- IV artesunate superior to IV quinine
  - 1461 patients (mostly adults) in Asia: mortality 15% vs. 11% (34.7% risk reduction)
  - 5425 children in Africa: mortality 10.9% vs. 8.5% (22.5% risk reduction)
  - Systematic reviews → similar risk reduction
- Drugs may also be administered rectally
- IV artesunate now FDA-approved

Dondorp, et al, Lancet 2005, 366, 717-25
Dondorp, et al, Lancet 2010, 376, 1647-57
Rosenthal, NEJM 2008, 358:1829-36

## Antimalarial drugs

- 4-aminoquinolines: Chloroquine, Amodiaquine, Piperaquine
- Quinine, Mefloquine, Halofantrine, Lumefantrine, Pyronaridine
- Antifolates: Sulfadoxine/Pyrimethamine, Trimethoprim/Sulfamethoxazole
- Artemisinins: Artesunate, Artemether, DHA
- Antibiotics: Doxycycline, Clindamycin
- Malarone
- Primaquine, Tafenoquine
- Key treatment regimen: ACTs

## The Vietnam war and the development of antimalarial drugs

- Malaria major problem for troops on all sides
- US Army- major drug development program, leading to development mefloquine
- China- Project 523 (established May 23, 1967)
  - Secret program during cultural revolution
  - 60 laboratories, >500 scientists
  - Investigation >2000 traditional Chinese medicines
  - Screening extracts from Artemisia annua (sweet wormword) led to identification qinghaosu
    - Outstanding activity against mouse malaria 1971
    - Excellent clinical activity reported early 1980s
    - Combination therapies validated in Thailand 1980s

Youyou Tu
Nobel Prize for Medicine, 2015

## Treatment of malaria in the USA

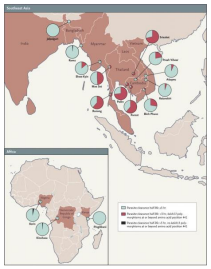
- Nonfalciparum malaria
  - Chloroquine (other drugs also effective)
  - Also Primaquine or Tafenoquine for vivax and ovale (after G6PD shown to be normal)
- Falciparum malaria
  - Coartem (Artemether-lumefantrine)
  - Malarone
  - Quinine plus Doxycycline (adults)
  - Quinine plus Clindamycin (children)
  - Mefloquine
- Severe disease:
  - IV Artesunate – now FDA approved
  - IV Quinidine – no longer available

## Antimalarial drug resistance

- Some degree of resistance seen with nearly all drugs
- High-level resistance
  - Chloroquine (but decreasing)
  - Antifolates (SP)
- Moderate resistance
  - Mefloquine, Amodiaquine
- Emerging resistance
  - Artemisinins and partner drugs

## Artemisinin resistance in SE Asia

- Decreased efficacy of artemisinins & ACTs
- Delayed parasite clearance
- Standard $IC_{50}$ assays do not correlate with phenotype
- Decreased activity in ring survival assay (RSA)
- Specific polymorphisms in kelch (K13) gene
- ACT resistance with loss of partner drugs
- Malaria problem modest in SE Asia



Ashley, et al., NEJM, 2014

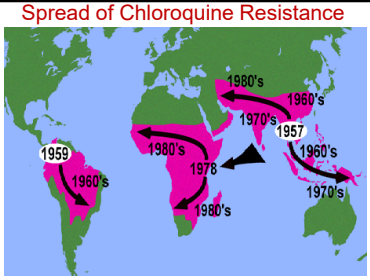
## Artemisinin resistance

- Delayed parasite clearance
  - In vivo
    - Persistent parasitemia on day 3
    - Parasite clearance $t_{½}$ > 5.5 h
  - In vitro: abnormal ring-survival assay
- Molecular marker: mutations in K13 gene
  - >100 different mutations have been seen
  - Most mutations not associated with ART R
  - WHO definitions for mutations mediating resistance:
    - Candidate/associated- Assoc. w/ delayed clearance in vivo or in vitro

| Validated | | Candidate or associated | |
|---|---|---|---|
| F446I | P553L | P441L | N537I/D |
| N458Y | R561H | G449A | G538V |
| M476I | P574L | C469F/Y | V568G |
| Y493H | C580Y | A481V | R622I |
| R539T | | R515K | A675V |
| I543T | | P527H | |

Rwanda, Cambodia, Uganda

## Spread of Chloroquine Resistance

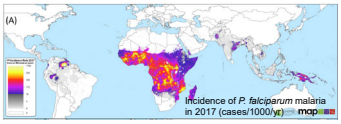



Why does drug resistance always emerge in SE Asia?

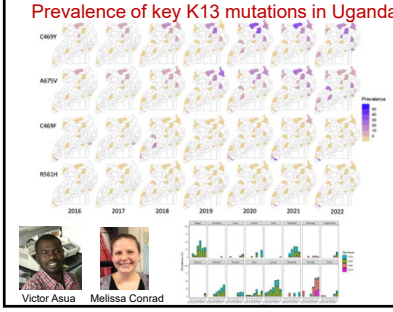
## Is artemisinin resistance a problem in Africa?

Our understanding in ~2018

- Clinical data:
  - Multiple ACTs show outstanding efficacy
  - No clear evidence for delayed parasite clearance
- Parasitological data
  - New RSA assay available: No evidence resistance
- Molecular data
  - Mutations associated with resistance in SE Asia not seen




## Prevalence of key K13 mutations in Uganda

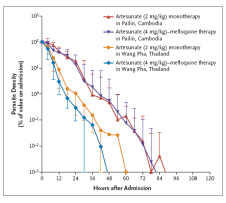


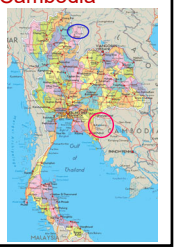


Victor Asua


Melissa Conrad

## Artemisinin "partial resistance"
## Delayed parasite clearance after tx with artesunate in Cambodia




Dondorp, et al., NEJM 361:455, 2009

## Is artemisinin resistance a problem in Africa?

Our understanding in ~2018

- Clinical data suggest: No
  - Multiple ACTs show outstanding efficacy
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- Parasitological data
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- Molecular data
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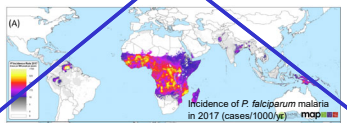
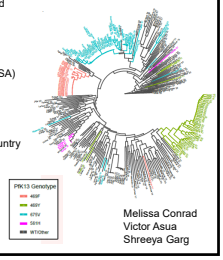



## Artemisinin partial resistance in Africa

- Five K13 mutations associated with R (delayed clearance) recently identified
- Rwanda: 561H
  - Prevalence up to ~20%
  - Delayed clearance
    - Clinical study
    - Enhanced survival in vitro (RSA)
- Uganda: 469Y, 469F, 561H, 675V
  - Delayed clearance clinically
  - Enhanced survival in vitro
- Eritrea: 622I
- Independent emergences in each country

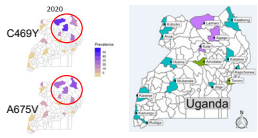



Uwimana, et al., Nat Med, 2020
Asua, et al., JID, 2021
Balikagala, et al., NEJM, 2021

Melissa Conrad
Victor Asua
Shreeya Garg

## Why did artemisinin resistance emerge in N. Uganda?

Emergence in districts that utilized IRS, but then stopped




Utilization of indoor residual spraying of insecticide (IRS)

Districts intensively studied:

- IRS every 6 months 2010-14 + once in 2017
- IRS beginning in 2015
- No IRS

Hypothesis: Resistance selection was facilitated by stopping IRS after a long period of sustained and effective malaria control, leading to malaria epidemics in non-immune populations.

Tumwebaze, et. al, Nat Commun, 2022
Conrad, et. al, submitted

## Antimalarial chemoprophylaxis in travelers: Summary

- Is prophylaxis really needed?
  - Many cities in endemic countries are not a risk
  - Cities in Africa and Indian subcontinent are high risk
  - Detailed information available from CDC (www.cdc.gov)
- Areas without chloroquine resistance: Chloroquine
- Areas with chloroquine resistant falciparum malaria
  - Mefloquine – older choice; toxicity concerns; contraindicated with psych disease or seizure disorder
  - Malarone – now usually the first choice, but expensive, especially for a long trip
  - Doxycycline – inexpensive; particularly for areas with multidrug resistance (esp. rural SE Asia)

## Insecticide classes for malaria control

- Pyrethroids- until recently the only class available in ITNs; major problem with resistance
- Organochlorines (DDT)- major problem with resistance
- Carbamates- expensive
- Organophosphates- expensive
- New combination insecticide strategies

Number of classes with vector resistance 2010-16

## New approaches to antimalarial chemotherapy

- Development of new drugs (slow)
- New combinations
  - Triple ACTs
- Different drugs for tx and prevention; Rotate drugs
- Monoclonal antibodies


Medicines for Malaria Venture
Van der Pluijm, et al., Lancet, 2020
Gaudinski, et al., NEJM, 2021

## Intermittent preventive therapy (IPT)

- Intermittent full treatment, regardless of infection status
- IPTp (pregnancy)
  - SP once per antenatal visit (up to monthly)
  - Policy across Africa
- IPTi (infants)
  - Usually following EPI schedule (not best-suited for malaria prevention)
  - Recently endorsed in Sierra Leone
- Seasonal malaria chemoprprevention (SMC)
  - West Africa
    - Seasonal malaria
    - Low prevalence drug resistance
  - Monthly tx children with SP/AQ for 3-4+ mo. (transmission season)
- Various approaches have shown good efficacy


## Malaria control

- Prompt effective therapy
- Other uses of drugs
  - Chemoprevention
  - Intermittent preventive therapy (IPT)
- Control of mosquito vectors
  - Personal protection (ITNs)
  - Indoor residual spraying (IRS)
- Malaria vaccine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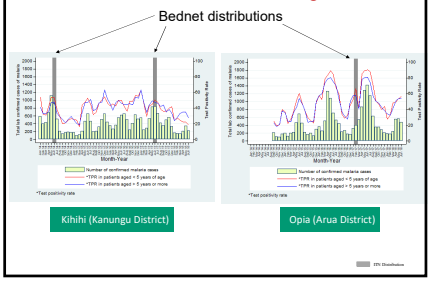
*Anopheles* mosquito

## Insecticide-treated bednets (ITNs)

- Bednets impregnated w/ pyrethrin insecticides
- Fairly inexpensive (~$7 retail)
- Fairly durable
- Clear benefits:
  - Significant (~20%) reductions in childhood mortality
  - No evidence for "delayed mortality"
- Generally provided free of charge
- Minimal increased ("rebound") risk after use

## Limited effects of ITNs in Uganda

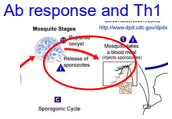



## Indoor residual spraying of insecticides (IRS)

- Considered highly effective in epidemic-prone areas (relatively low transmission).
- Appears to be safe
- WHO recommendations for IRS
  - Areas with unstable transmission
  - Areas with moderate seasonal transmission
- Insecticide resistance limits efficacy DDT & permethrins; other insecticides much more expensive.
- Now used in areas of high transmission, but use limited by high cost.

## RTS,S: the new malaria vaccine

- RTS,S/ASO2A
- *P. falciparum* CSP antigen
- CSP fused to HBsAg with new adjuvant (ASO2A – emulsion containing two immunostimulants)
- Vaccine elicited strong Ab response and Th1 cellular responses



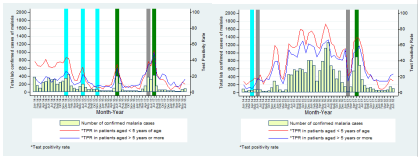
## New bednets to reverse pyrethroid resistance

- Piperonyl butoxide (PBO): pyrethroid "synergist", inhibiting rapid metabolism by resistant mosquitoes
  - New LLINs contain a pyrethroid + PBO
  - Trials in Tanzania, Uganda: significant decreases in malaria burden compared to standard LLIN
- Pyriproxyfen: insect growth regulator
  - New LLINs contain a pyrethroid + pyriproxyfen
  - Trial in Burkina Faso: significant decreases in malaria burden compared to standard LLIN

| Malaria prevalence 4 months after intervention: | |
|---|---|
| Standard LLIN | 553/997 (55%) |
| PBO LLIN | 445/971 (46%) |
| Standard LLIN plus IRS | 383/994 (39%) |
| PBO LLIN plus IRS | 353/955 (37%) |

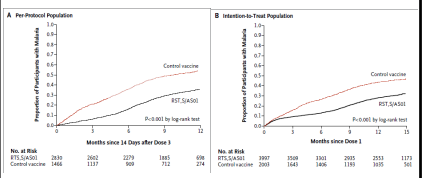
Protopopoff, et al. Lancet 2018; 391: 1577–88
Staedke, et al. Lancet 2020; 395; 1292-1303
Tiono, et al. Lancet 2018; 392: 569-580

## Dramatic effects of IRS in Uganda




Decreased impact of IRS recently:
Ineffective insecticide?
Changes in vector species?

## RTS,S vaccine Phase 3 trials




3 monthly doses to children 5-17 mo. age at enrollment

- Vaccine efficacy ~30-50% against malaria and ~45% against severe malaria
- Results short-lived; boosting required
- Decreased efficacy in youngest children

RTS,S Clinical Trials Partnership, NEJM 2011;365:1863
RTS,S Clinical Trials Partnership, Lancet 2015;386:31

## Malaria control

- Prompt effective therapy
- Other uses of drugs
  - Chemoprevention
  - Intermittent preventive therapy (IPT)
- Control of mosquito vectors
  - Personal protection (ITNs)
  - Indoor residual spraying (IRS)
- Malaria vaccine

## Malaria control

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## RTS,S endorsed by WHO

- Requires multiple doses, boosting
- Widespread availability is years away
- Will vaccine pull resources from other control tools?

**WHO recommends groundbreaking malaria vaccine for children at risk**

Historic RTS,S/AS01 recommendation can reinvigorate the fight against malaria

6 October 2021 | News release | Geneva | Reading time: 3 min (650 words)

GSK, PATH, and Bharat Biotech sign product transfer agreement to help ensure long-term supply of RTS,S/AS01E malaria vaccine

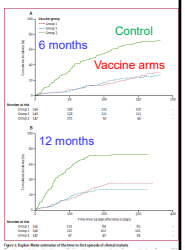
For media and investors only

Issued: London, UK

- Bharat Biotech to produce antigen for world's first vaccine against Plasmodium falciparum malaria following technology transfer, to help ensure long-term sustainable supply

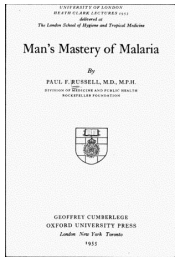
## Another CSP-based vaccine: R21

- Different adjuvant and different presentation of Ag compared to RTS,S
- Protective efficacy ~75% at 6 mo. and 1 yr. (3 dose regimen)
- Single booster maintained protection in yr 2
- Will be available in large quantity sooner than RTS,S
- Not yet approved by WHO




Datoo, et al., Lancet, 2021;397:1809-1818
Datoo, et al., Lancet Infect Dis. 2022;22:1728-1736

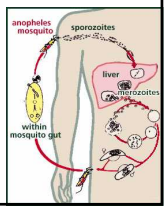
## Can malaria be eradicated?





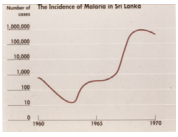
## Other malaria vaccine strategies

- Antigens from different parasite stages
  - Sporozoite
  - Erythrocytic
  - Gametocyte & mosquito stages
- Different types of vaccines
  - Peptide
  - DNA, mRNA
  - Attenuated sporozoites
- Monoclonal Abs




## Malaria eradication- history

- 1940s- regional elimination campaigns
- 1955- Global Malaria Eradication Program
  - Eradicated from Europe, N. America, Parts of Caribbean, S. America, Asia
  - Success, followed by rebound on Indian sub-continent
  - No significant impact in Africa
  - Techniques:
    - DDT spraying
    - Draining swamps
    - CQ-medicated salt
- Program abandoned-1969
  - Replaced by control agenda




## Transgenic mosquitoes to prevent malaria

- New technologies show increasing likelihood of success
  - Gene drive
- Requirements
  - Develop anopheline mosquitoes that cannot transmit malaria (many species)
  - Provide these mosquitoes with a survival advantage over all other mosquitoes
  - Figure out how to spread these mosquitoes around the world
  - Don't create an environmental catastrophe


## Can malaria be eradicated? The shrinking malaria map