

Malaria Update

SFR Utbildningsdag 26/9

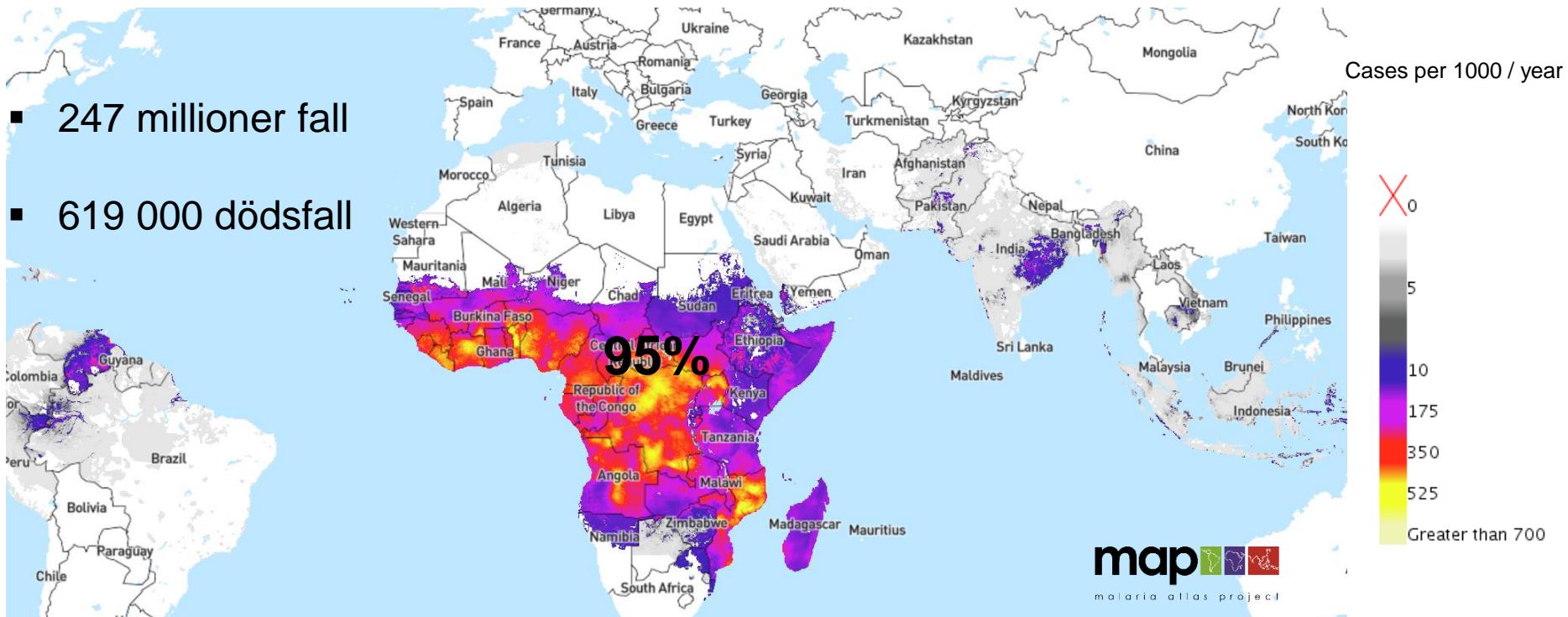


Katja Wyss
PhD Infektionsläkare
ME Infektionssjukdomar
Karolinska Universitetssjukhuset

Malaria global situation

- WHO rapport 2022:

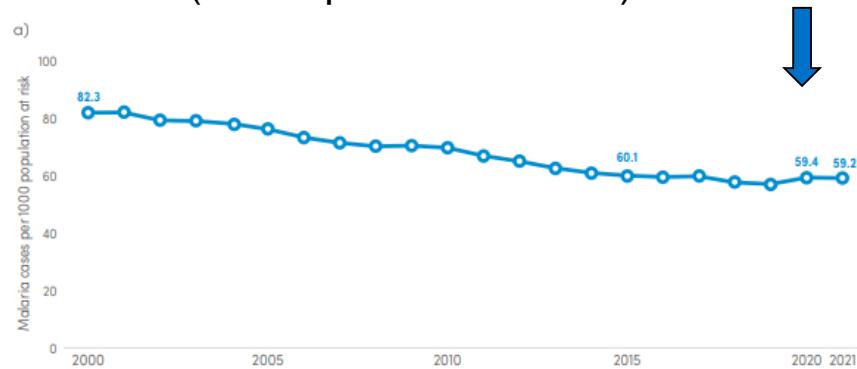
- 247 millioner fall
- 619 000 dödsfall



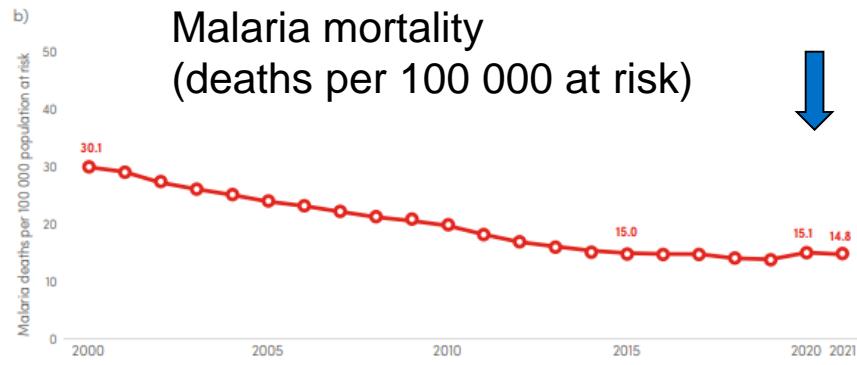
Global trend



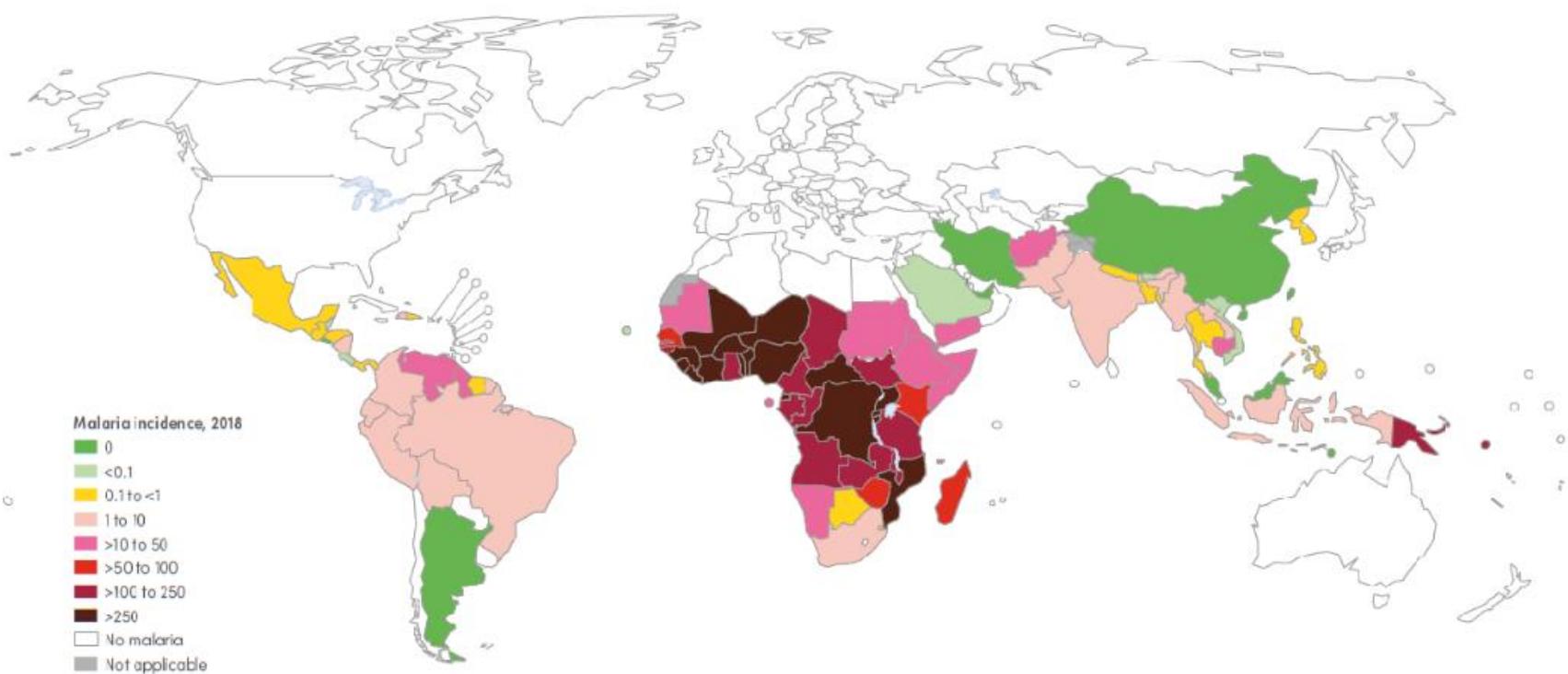
Malaria case incidence
(cases per 1000 at risk)



Malaria mortality
(deaths per 100 000 at risk)

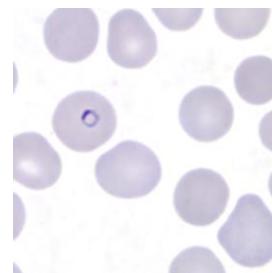


Endemiska länder

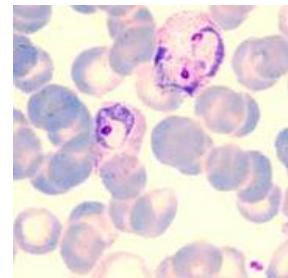


Parasiten - Plasmodium

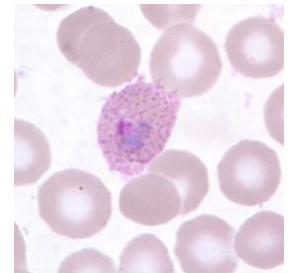
- Protozo (encellig)
- 120 arter
- 5 infekterar människan



P. falciparum

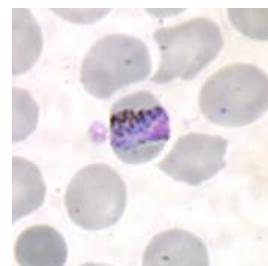


P. vivax

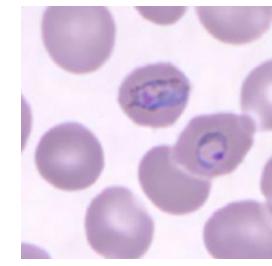


P. ovale

*Förekommer även mindre
utbrott med "simian malaria"*

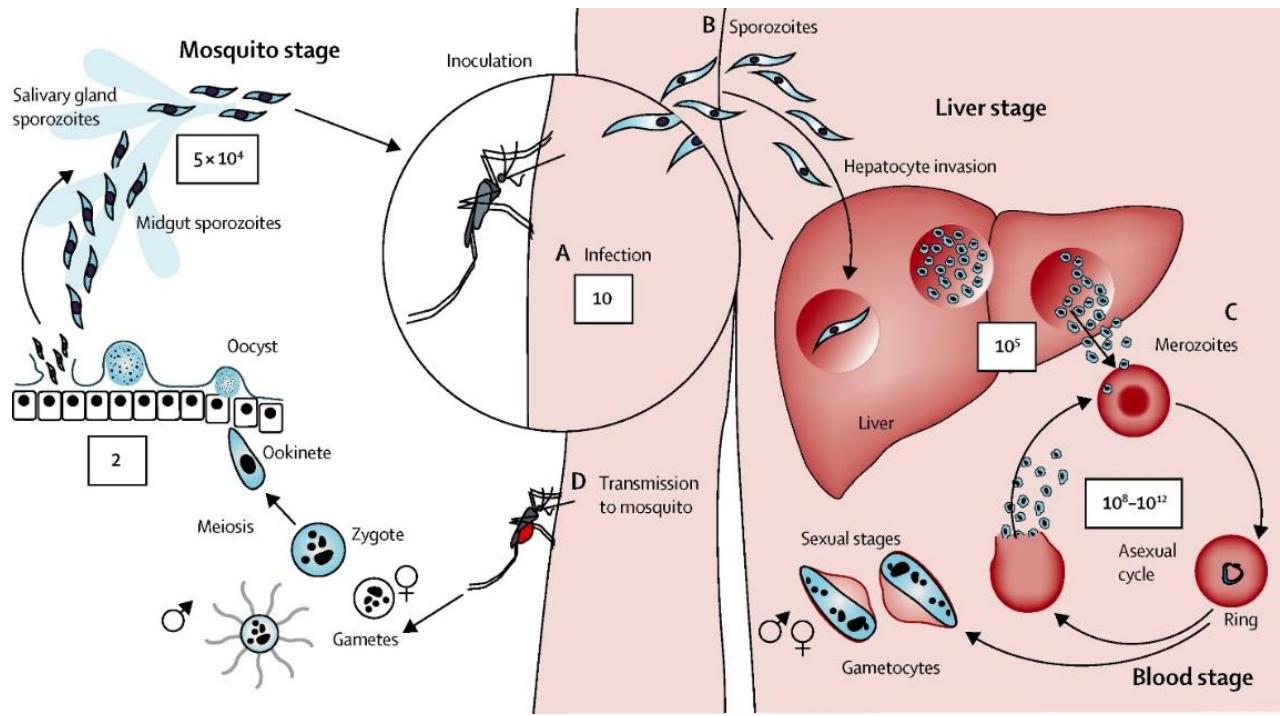


P. knowlesi



P. malariae

Malariaparasitens livscykel



Plasmodium falciparum



Foto: Lennart Nilsson



Alternativa transmissionsvägar

- Transfusion av blodprodukter
 - Räcker med bara 10 infekterade rdbk
 - Överförs i alla fraktioner (erytrocyter, plasma, trombocyter)
 - Alla Plasmodium arter kan överleva i lagrat blod, även vid frysning
- Kongenital malaria
- Organ donation



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Rare malaria death of girl in northern Italy puzzles doctors

© 5 September 2017

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Förekommer fall inom sjukvården!

2016-2018 6 fall av sjukhus associerad malaria i EU



Malaria i Sverige

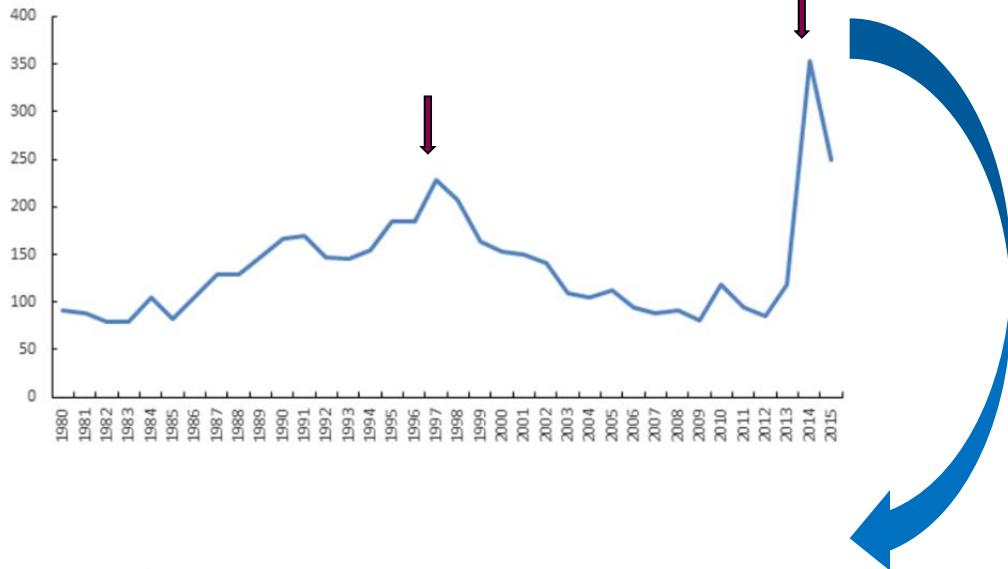
Nationell bevakning sedan 1987 -
Folkhälsomyndigheten

Anmälningsplikt

100-300 fall/år



Antal amälda fall 1980-2015



Figur 1. Antalet rapporterade fall av malaria under åren 2013–2022.

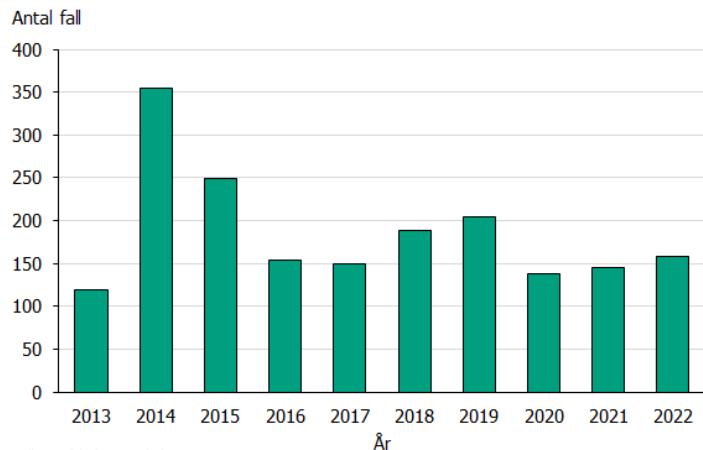
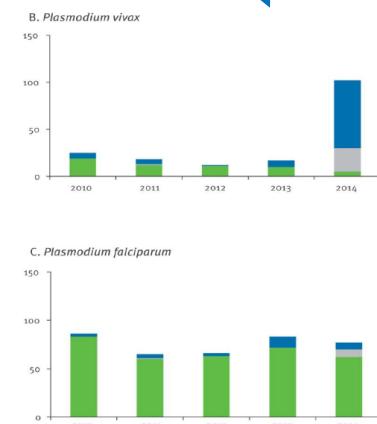
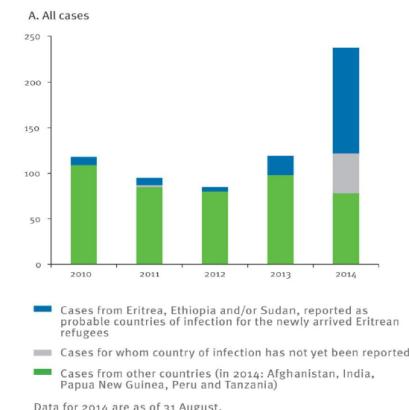
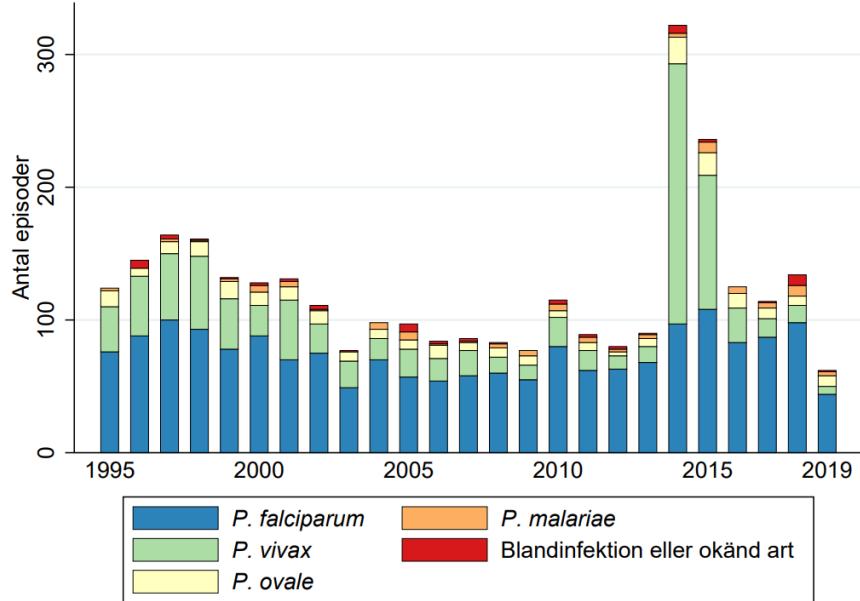
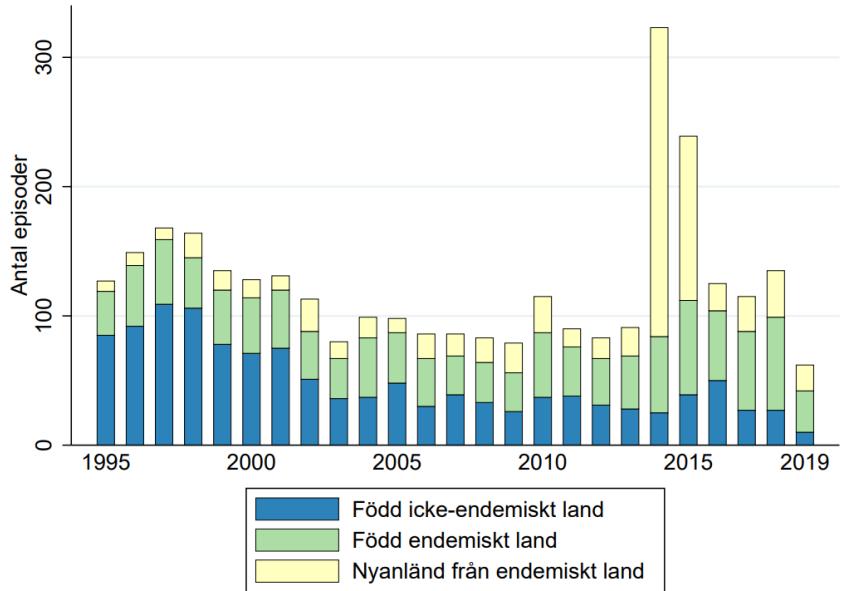


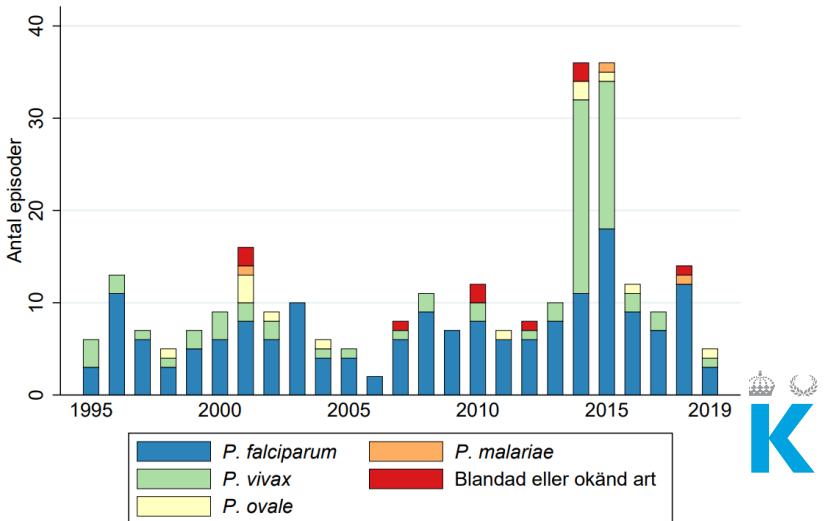
FIGURE 2
Number of malaria cases, by origin of infection, reported per year to the Public Health Agency, Sweden 2010–14 (n=654)



Malaria i Sverige: Patientursprung och species

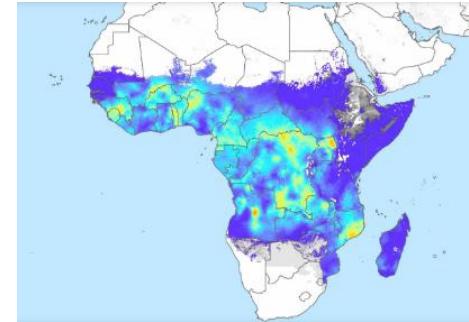


Allvarliga malaria fall
~8% ($n=238/3069$)



Studie 2019-2020

Screening av migranter



Vuxna och barn från sub-Sahara Afrika

Samma dag

Malaria antigen snabbtest

CareStart™ Malaria Pf/PAN (HRP2/pLDH) Ag Combo RDT

Hemoglobin concentration (Hemocue™)



Senare

Realtids PCR för *P. falciparum*, *P. ovale*, *P. malariae* och
P. vivax

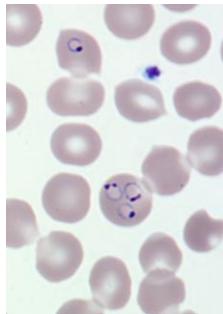
Serologi med ELISA and Luminex



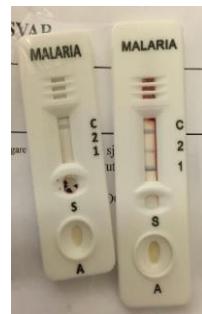
Alla malariapositiva individer kallas till inf-/barn-mottagning
för bekräftande prov och behandling

Malaria - diagnostik

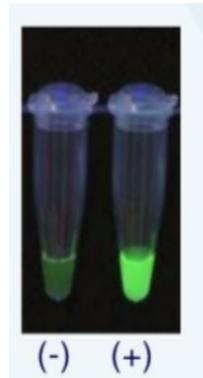
Mikroskopi



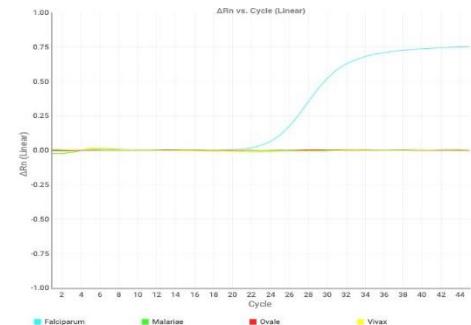
Snabbtest



LAMP



PCR



-10-50 parasiter/ μ l
-alla arter, kvantitativt
-aktuell infektion

-40-100 parasiter/ μ l
-P falc / non-falcip
-pLDH *Plasmodium*
spec Ag / HRP2 –*P falc*
-kan vara falskt negativ!

-4-10 parasiter/ μ l
-ej art specifik
-ej kvantitativt

-0,1-10 parasiter/ μ l
-alla arter

Malaria parasite prevalence in Sub-Saharan African migrants screened in Sweden: a cross-sectional study

Andreas Wångdahl,^{a,b} Rebecca Tafesse Bogale,^a Isabelle Eliasson,^a Joanna Broumou,^b Fariba Faroogh,^a Filip Lind,^a Ganna Vashchuk,^a Adina Hildell,^a Suzanne Fransson,^a Emil Hallberg,^a Isabelle Grip,^a Irene Nordling,^c Angelica Gervin,^d Shelan Kaitoly,^d Berhane Tekleab,^d Katja Wyss,^{a,c} Ana Requena-Méndez,^{a,c,g} Olof Hertting,^{e,f} and Anna Färnert^{a,c,*}



^aDivision of Infectious Diseases, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

^bDepartment of Infectious Diseases, Västerås Hospital, Västerås, Sweden

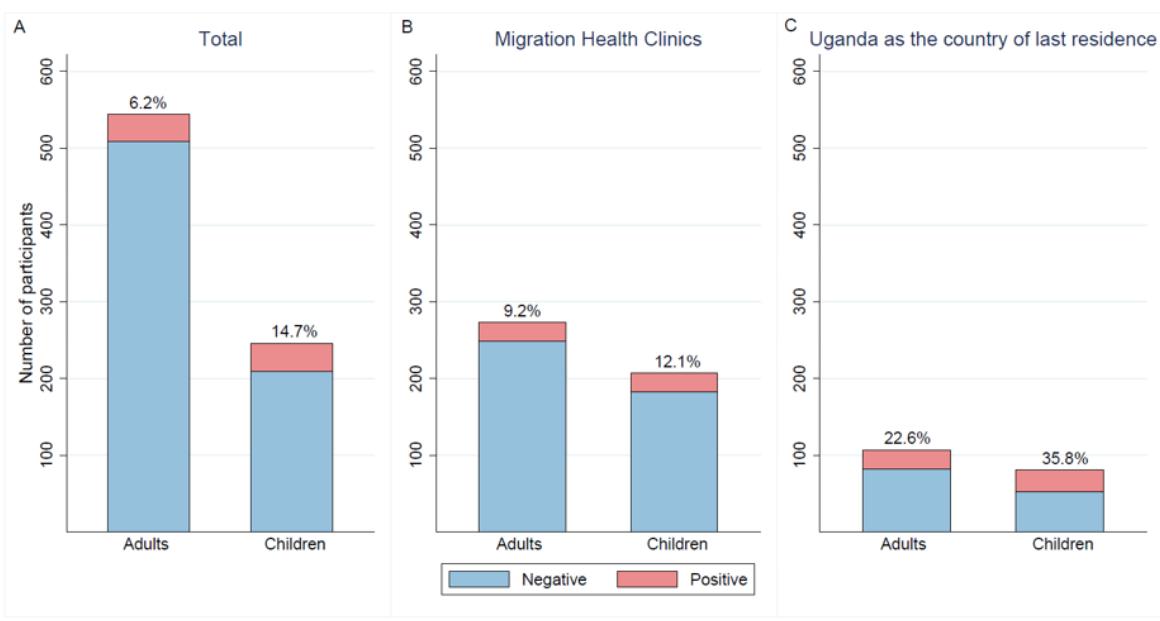
^cDepartment of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden

^dRissne Vårdcentral, Migration Health Centre, Region Stockholm, Stockholm, Sweden

^ePaediatric Infectious Diseases, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden

^fDepartment of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

^gBarcelona Institute for Global Health (ISGlobal), University of Barcelona, Spain



- Antal screenade: 789
- PCR positiva: 71 (9%)
- 46 *P. falciparum*
- Kvotflyktingar från Uganda: 53 (28%)
- Fall i familjer till PCR positiva: 47 (60%)
- Bärarskap påvisat upp till 386 dagar efter ankomst

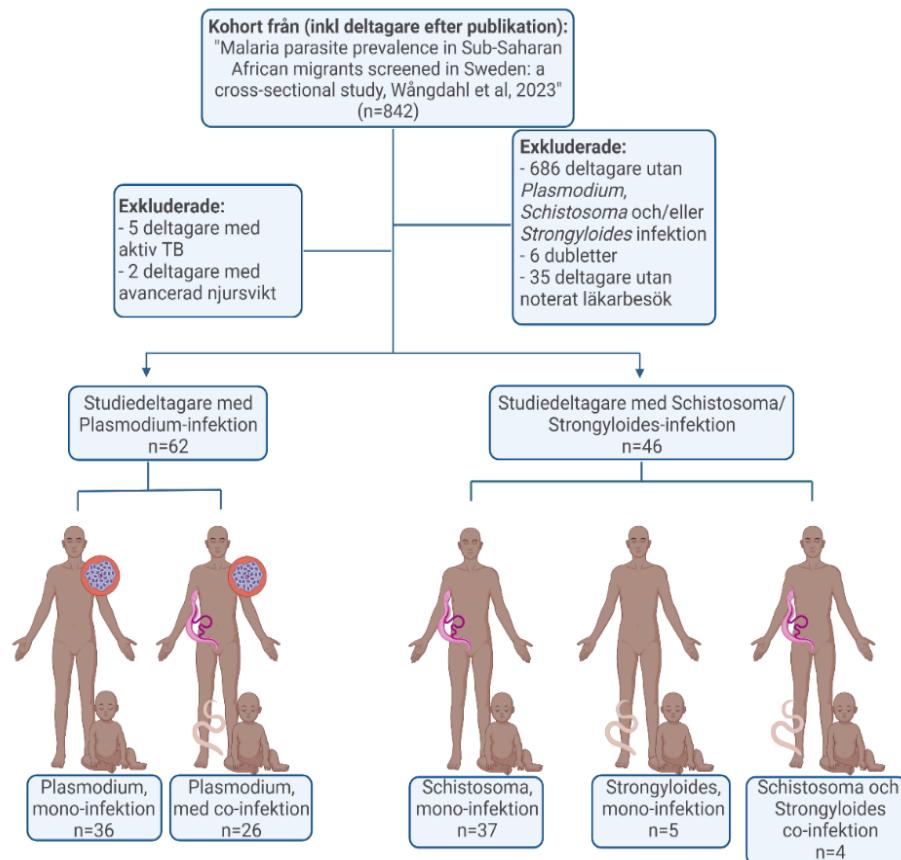
Konsekvenser av långvarigt asymptomatiskt bärarskap?

- Komplikationer under graviditet (Okell et al 2012)
- Anemi (Sifft et al 2016)
- Kognitiv påverkan (Fernando et al 2010)
- Symptomatisk sjukdom (Njama-Meya 2004)
- Burkitts lymphom (Ellis et al 2021)
- Non-burkitts lymphomas? (Bates et al 1997, Bedu-Addo 2002)
- Tropical hypersplenomegaly syndrome /Hyperreactive Malaria Splenomegaly (Leoni et al 2015)

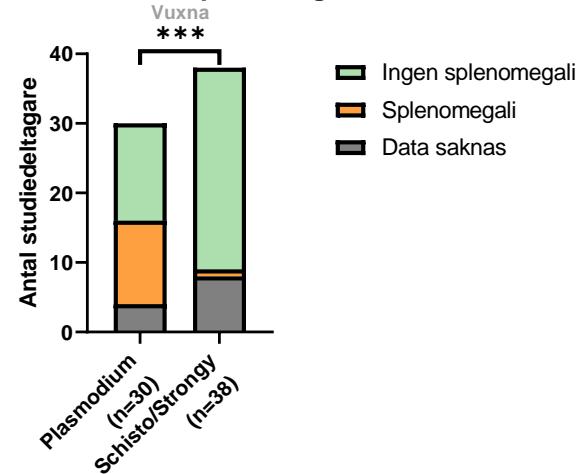


Figure 2 African patient with splenomegaly seen at the Centre for Tropical Diseases, Negrop.

Ökad förekomst av splenomegali hos migranter med submikroskopiskt bärarskap av *Plasmodium*



Förekomst av splenomegali

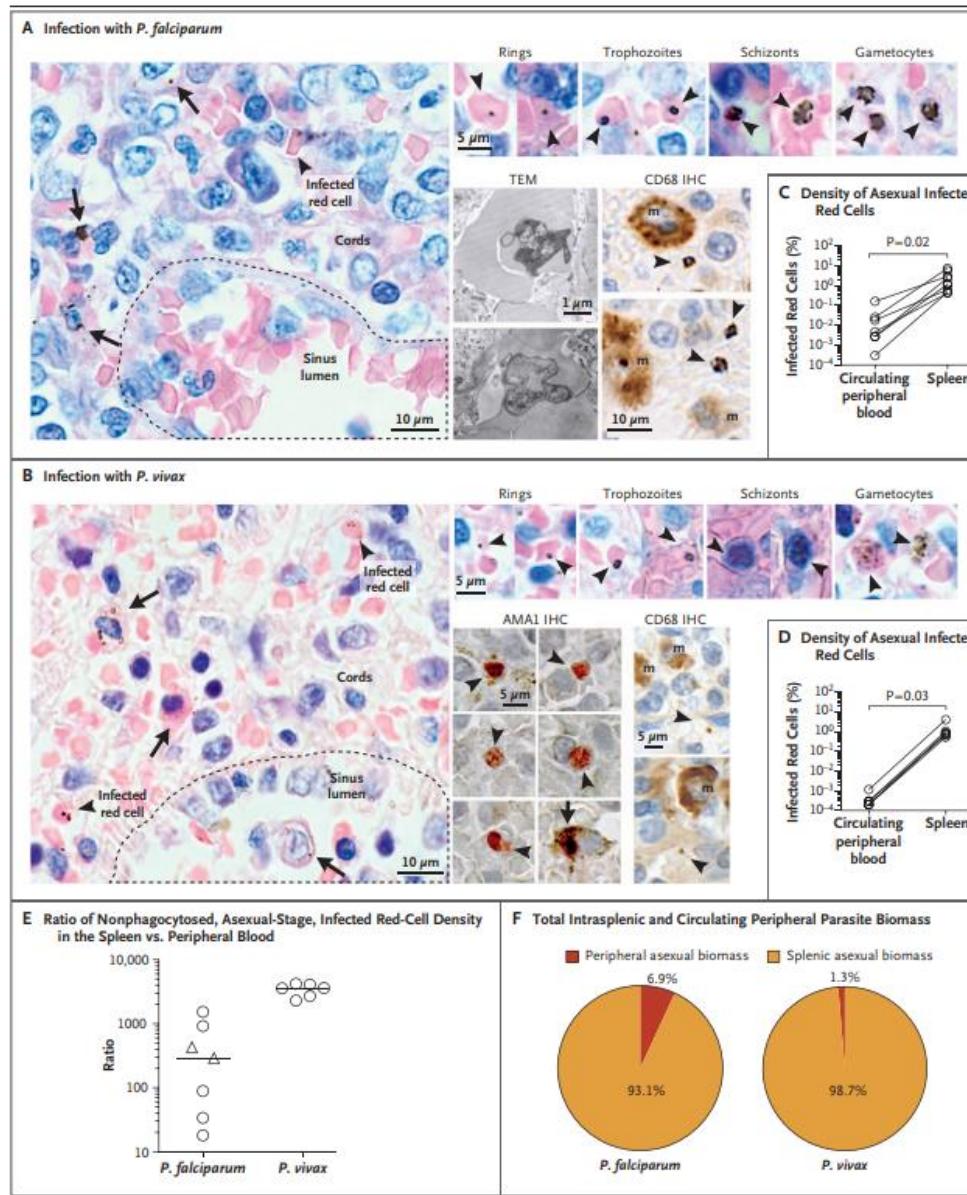


Splenomegaly rate

Plasmodium group: 16/62=26%
 Control group=1/46=2%

Hyperreactive Malaria Splenomegali
 Full HMS 2/16
 Pre-HMS 7/16

Dold malaria reservoir i mjälten vid kronisk infektion?

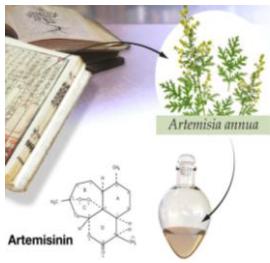


Utmaningar

Resistens mot myggmedel

ITNs hittills viktigaste preventiva strategin mot malaria

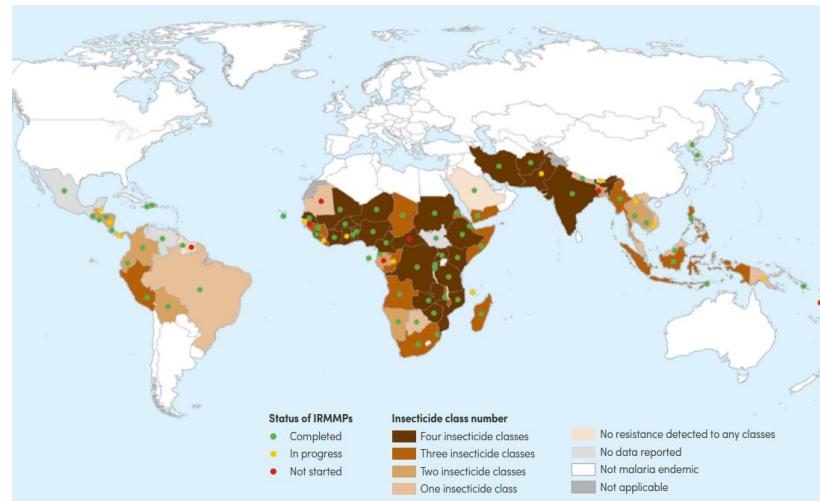
Myggor resistenta mot myggmedel (ffa pyretroider) rapporteras från 88 länder
-WHO 2021



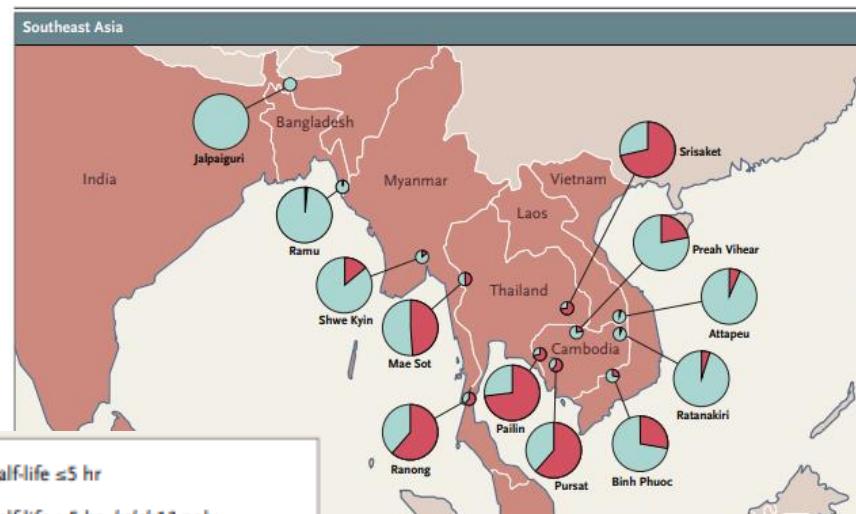
Resistens mot artemisinin

Artemisinin-Resistant Malaria in Western Cambodia
-Noedl et al NEJM 2008

Spread of Artemisinin Resistance in *P falciparum* Malaria -White et al NEJM 2014

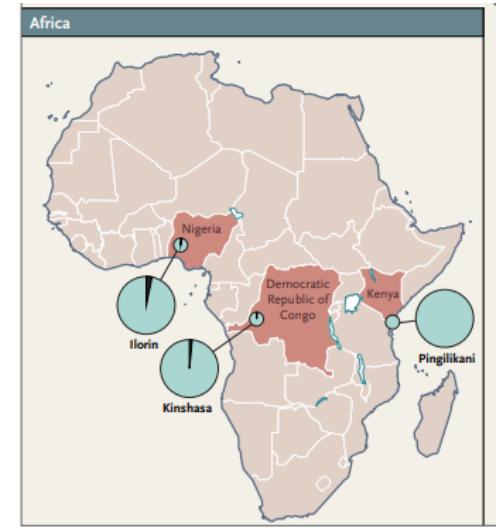


Number of classes to which resistance was confirmed in at least one malaria vector, 2010–2020



Dondorp Nature review 2010

Nytt hot? -ART resistens i Afrika



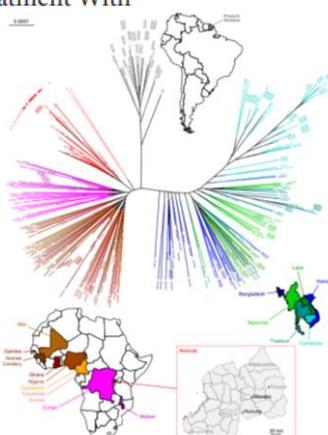
The Journal of Infectious Diseases

BRIEF REPORT

High Prevalence of *Plasmodium falciparum* K13 Mutations in Rwanda Is Associated With Slow Parasite Clearance After Treatment With Artemether-Lur

Judith Strainer,¹ Preetam Gandhi,
Esther K. Schmid²*

¹Novartis Institutes for Biomedical Research, Basel, Switzerland



nature microbiology

Analysis

<https://doi.org/10.1038/s41564-023-01461-4>

Plasmodium falciparum resistant to artemisinin and diagnostics have emerged in Ethiopia

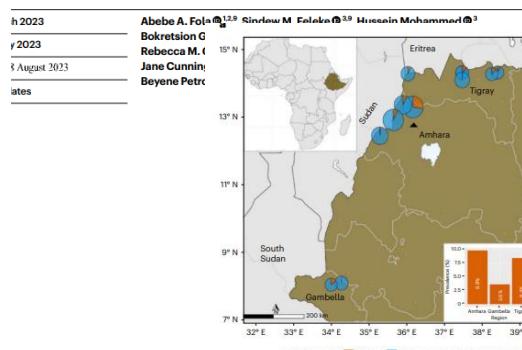


Fig. 1. a, Phylogenetic tree of K13 622I mutations. b, Spatial distribution of K13 622I mutations at the district (left) and regional (right) levels. Colours indicate mutation status and pin chart size is proportional to sample size per district. The black triangle indicates the location where K13 622I mutation was reported previously. c, Prevalence of non-synonymous mutations across the K13 gene, coloured according to WHO

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Evolution of Partial Resistance to Artemisinins in Malaria Parasites in Uganda

Melissa D. Conrad, Ph.D., Victor Asua, M.Sc., Shreeya Garg, B.S., David Giesbrecht, Ph.D., Kararmoko Niaré, Ph.D., Sawyer Smith, B.S., Jane F. Namuganga, M.H.S., Thomas Katairo, M.Sc., Jennifer Legac, B.S., Rebecca M. Crudale, B.S., Patrick K. Tumwebaze, M.Sc., Samuel L. Nsobya, Ph.D., Roland A. Cooper, Ph.D., Moses R. Kamya, M.B., Ch.B., Ph.D., Grant Dorsey, M.D., Ph.D., Jeffrey A. Bailey, M.D., Ph.D., and Philip J. Rosenthal, M.D.

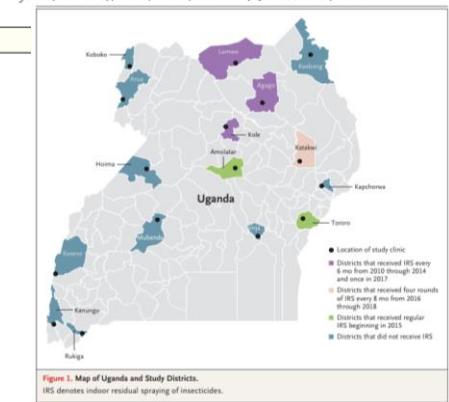


Figure 1. Map of Uganda and Study Districts. IRS denotes indoor residual spraying of insecticides.

Och bland resenärer?

pfk13-Independent Treatment Failure in Four Imported Cases of *Plasmodium falciparum* Malaria Treated with Artemether-Lumefantrine in the United Kingdom

Colin J. Sutherland,^{a,b} Paul Lansdell,^a Mandy Sanders,^c Julian Muwanguzi,^b Donelly A. van Schalkwyk,^b Harpakash Kaur,^b Debbie Nolder,^a Julie Tucker,^a Hayley M. Bennett,^c Thomas D. Otto,^c Matthew Berriman,^c Trupti A. Patel,^d Roderick Lynn,^e Effrosyni Gkrania-Klotsas,^f Peter L. Chiodini^{a,d}

Public Health England Malaria Reference Laboratory, London School of Hygiene & Tropical Medicine, London, United Kingdom;^a Department of Immunology & Infection, Faculty of Infectious & Tropical Diseases, London School of Hygiene & Tropical Medicine, London, United Kingdom;^b Wellcome Trust Sanger Institute, Hinxton, United Kingdom;^c Hospital for Tropical Diseases, London, United Kingdom;^d Haematology Department, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; Infectious Diseases Department, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom

ABSTRACT We present case histories of four patients treated with artemether-lumefantrine for falciparum malaria in UK hospitals in 2015 to 2016. Each subsequently presented with recurrent symptoms and *Plasmodium falciparum* parasites within 6 weeks of treatment with no intervening travel to countries where malarial endemic. Parasite isolates, all of African origin, harbored variants at some candidate resistance loci. No evidence of *pfk13*-mediated artemisinin resistance was found. vigilance for signs of unsatisfactory antimalarial efficacy among imported cases of malaria is recommended.

Clinical Infectious Diseases

BRIEF REPORT

Circulation of an Artemisinin-Resistant Malaria Lineage in a Traveler Returning from East Africa to France

Romain Coppée,^{1,2,3} Justine Bailly,^{1,2,4} Véronique Sarrasin,^{1,2} Bertrand Vianou,² Boris-Enoch Zinsou,² Edith Mazars,² Hugues Georges,² Samia Hamane,⁵ Rose-Anne Lavergne,² Eric Dannaoui,² Betty Balikagala,⁶ Naoyuki Fukuda,⁶ Emmanuel I. Odongo-Aginya,⁶ Toshihiro Mita,⁶ Sandrine Houzé,^{1,2} and Jérôme Clain,^{1,2}; on behalf of the French National Malaria Reference Center Study Group

¹Université de Paris, IRD, MERIT, Paris, France; ²Centre National de Référence du Paludisme, AP-HP, Hôpital Bichat-Claude Bernard, Paris, France; ³Institut de Recherche Clinique du Bénin, Cotonou, Bénin; ⁴Laboratoire de microbiologie, Pôle de Biologie-hygiène, Centre Hospitalier de Valenciennes, Valenciennes, France; ⁵Service de Réanimation Médicale et Maladies Infectieuses, Hôpital Chateliez, Tourcoing, France; ⁶Laboratoire de Parasitologie-Mycologie, AP-HP, Groupe Hospitalier Saint-Louis Lariboisière Fernand-Widal, Paris, France; ⁷Laboratoire de Parasitologie-Mycologie, Institut de Biologie, Centre Hospitalier Universitaire de Nantes, Nantes, France; ⁸Laboratoire de Parasitologie-Mycologie, AP-HP, Département de Microbiologie, Hôpital Européen Georges Pompidou, Paris, France; ⁹Department of Tropical Medicine and Parasitology, School of Medicine, Juntendo University, Hongo, Bunkyo-ku, Tokyo, Japan; and ¹⁰Faculty of Medicine, Gulu University, Gulu, Uganda

Clinical Infectious Diseases
MAJOR ARTICLE



High Rate of Treatment Failures in Nonimmune Travelers Treated With Artemether-Lumefantrine for Uncomplicated *Plasmodium falciparum* Malaria in Sweden: Retrospective Comparative Analysis of Effectiveness and Case Series

Klara Söndén,¹ Katja Wyss,^{1,2} Irina Joyev,³ Antero Vieira da Silva,⁴ Anton Pohanka,^{4,5} Muhammad Asghar,¹ Manijeh Vafa Homann,¹ Lars L. Gustafsson,^{4,5} Urban Hellgren,^{4,5} and Anna Färnert,^{1,6}

¹Unit of Infectious Diseases, Department of Medicine Solna, Karolinska Institutet; ²Department of Emergency Medicine, Karolinska University Hospital Solna; ³Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet; ⁴Department of Clinical Pharmacology, Karolinska University Hospital Huddinge; ⁵Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska Institutet; ⁶Department of Infectious Diseases, Karolinska University Hospital; and ⁷Unit of Infectious Diseases, Department of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden



Journal of Travel Medicine, 2023, 1–8
<https://doi.org/10.1093/jtm/taad114>
Original Article

Original Article

Emergence of artemisinin-based combination treatment failure in patients returning from sub-Saharan Africa with *P. falciparum* malaria

Tamar Grossman,¹ PhD Dr¹, Julia Vainer, MSc Dr¹, Yael Paran, MD^{2,3}, Liora Studentsky, MSc Dr¹, Uri Manor,^{1,2} MD Professor^{3,4}, Ron Dzikowski, PhD Professor⁵ and Eli Schwartz, MD, DTMH^{3,4}

¹Parasitology Reference Laboratory, Public Health Laboratories—Jerusalem (PHL-J), Public Health Services (PHS), Ministry of Health (MOH), Jerusalem 913402, Israel, ²Infectious Disease Department, Tel Aviv Sourasky Medical Center, Tel Aviv 64239, Israel, ³Faculty of Medicine, Tel Aviv University, Tel Aviv 69978, Israel, ⁴The Center for Geographic Medicine, Sheba Medical Center, Tel HaShomer 5262000, Israel and ⁵Department of Microbiology & Molecular Genetics, The Kuvim Center for the Study of Infectious and Tropical Diseases, IMRIC, The Hebrew University-Hadassah Medical School, Jerusalem 91120, Israel

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Submitted 11 July 2023; Revised 15 August 2023; Accepted 18 August 2023



Figure 5. The geographic distribution of Pfcr13 P76S status of 63 patients returning from Africa; place of travel and associated relative frequency of Pfcr13 mutation P76S in patients arriving from Africa ($n = 63$; seven patients who had visited more than one area were not included); circle size is in proportion to the number of patients from a country; maps were generated using Microreact,¹⁹ a dynamic version can be found at <https://microreact.org/project/xAWjgrHIEVi8mhlBLjaeZh-fg-5-geographic-distribution-and-pfcr13-p76s>

AL-treatment failure -When to suspect resistance?

Early failure: residual parasites by microscopy day 3

Late treatment failure: Clinical and laboratory-confirmed malaria recrudescence (positive blood smear) *reappearing 7–42 days after clinical and microscopy negative interval.*

Because artemisinins are fast-acting, early failures suggest artemisinin resistance, while late failures could result from a reduced effectiveness of artemisinin or lumefantrine, or both.

How to treat?

- Prolonged (5-6 days) AL
- Switch to Atovaquone+Proguanil /Mefloquine
- Triple combination? ART -lumefantrine+amodiaquine dihydroART-piperaquine+mefloquine

P. falciparum HRP2/3 gen deletion

CareStart pLDH Malaria (Pf-pLDH/pan-pLDH)

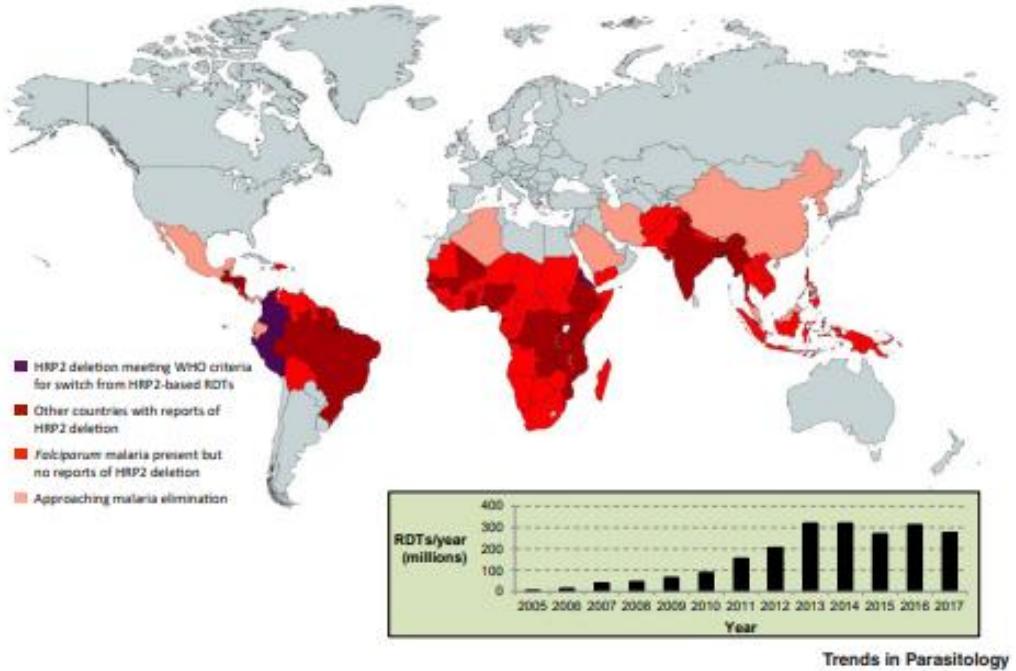
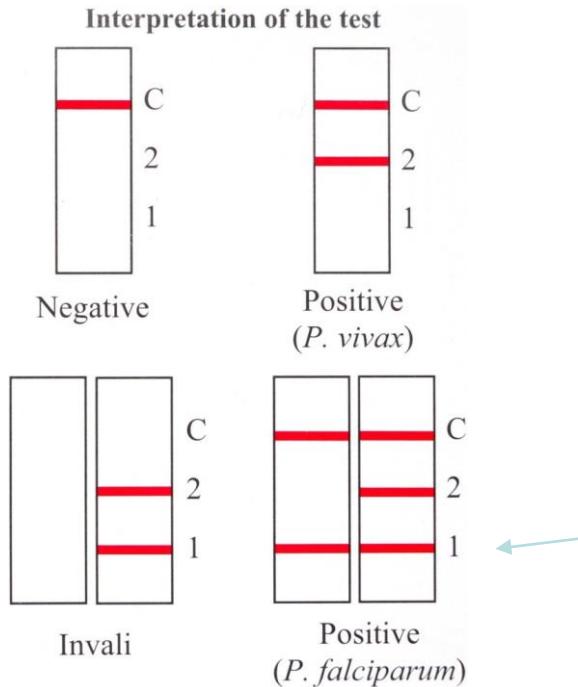
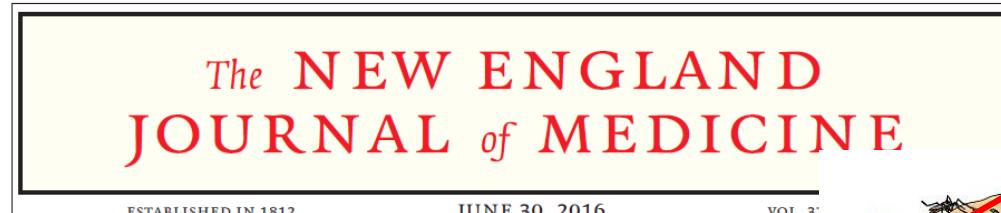


Figure 4. Deployment of Malaria Rapid Diagnostic Tests (mRDTs): Reports of Histidine-Rich Protein 2 (HRP2) Deletion and Overall Supply of mRDTs Per Year.

The map shows the global distribution of falciparum malaria (identifying countries nearing malaria elimination) and illustrates countries with reports of HRP2 deletion^{vii}, including Peru, Columbia, and Eritrea, where World Health Organisation (WHO) criteria for switching from HRP2-based mRDTs have been met. The map was created with mapchart.net. The inset graph shows the annual supply of all mRDTs from 2005 to 2017 in millions (data from WHO Malaria Reports^{vi,ix}).

Nytt hopp?



Seven-Year Efficacy of RTS,S/AS01 Malaria V among Young African Children

Ally Olotu, Ph.D., Gregory Fegan, Ph.D., Juliana Wambua, M.Sc., George Nyangwama, Amanda Leach, M.R.C.P.C.H., Marc Lievens, M.Sc., David C. Kaslow, M.D., Patricia Njau, Kevin Marsh, F.R.C.P., and Philip Bejon, Ph.D.

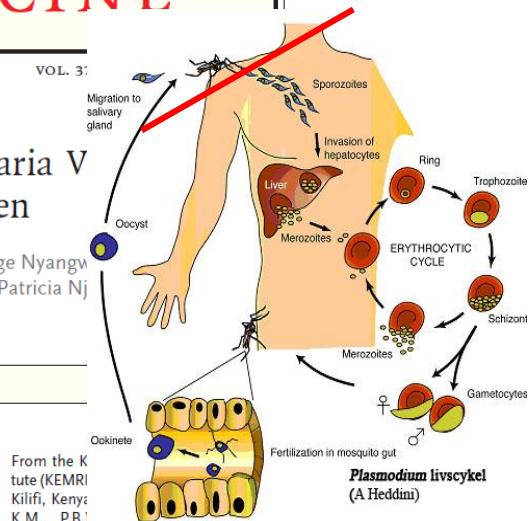
ABSTRACT

BACKGROUND

The candidate malaria vaccine RTS,S/AS01 is being evaluated in order to inform a decision regarding its inclusion in routine vaccination schedules.

METHODS

We conducted 7 years of follow-up in children who had been randomly assigned, at 5 to 17 months of age, to receive three doses of either the RTS,S/AS01 vaccine or a rabies (control) vaccine. The end point was clinical malaria (temperature of $\geq 37.5^{\circ}\text{C}$ and infection with *Plasmodium falciparum* of >2500 parasites per cubic millimeter). In an analysis that was not prespecified, the malaria exposure of each child was estimated with the use of information on the prevalence of malaria among residents within a 1-km radius of the child's home. Vaccine efficacy was defined as 1 minus the hazard ratio or the incidence-rate ratio, multiplied by 100, in the RTS,S/AS01 group versus the control group.



From the KEMRI-Wellcome Trust Research Programme (KEMRI Kilifi, Kenya; K.M., P.B.), Bagamoyo, Tanzania (A.O.); the Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom (G.F., K.M., P.B.); GlaxoSmithKline Vaccines, Ware, Belgium (A.L., M.L.); and PATH, Seattle (D.C.K.). Address reprint requests to Dr. Bejon at the KEMRI-Wellcome Trust Research Programme, P.O. Box 230, Kilifi, Kenya, or at pbejon@kemri-wellcome.org.

N Engl J Med 2016;374:2519-29.
DOI: 10.1056/NEJMoa1515257

-> Mosquirix™ rekommenderas av WHO sedan Okt 2021 som storskalig bekämpning av malaria bland barn i medel och högendemiska länder

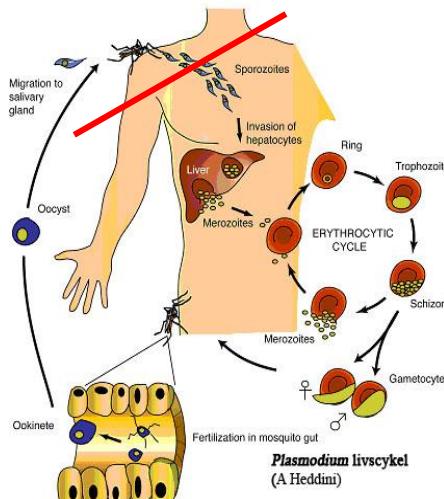
Efficacy and immunogenicity of R21/Matrix-M vaccine against clinical malaria after 2 years' follow-up in children in Burkina Faso: a phase 1/2b randomised controlled trial



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Summary

Background Malaria is a leading cause of morbidity and mortality worldwide. We previously reported the efficacy of the R21/Matrix-M malaria vaccine, which reached the WHO-specified goal of 75% or greater efficacy over 12 months in the target population of African children. Here, we report the safety, immunogenicity, and efficacy results at 12 months following administration of a booster vaccination.



80% efficacy
after 3 doses

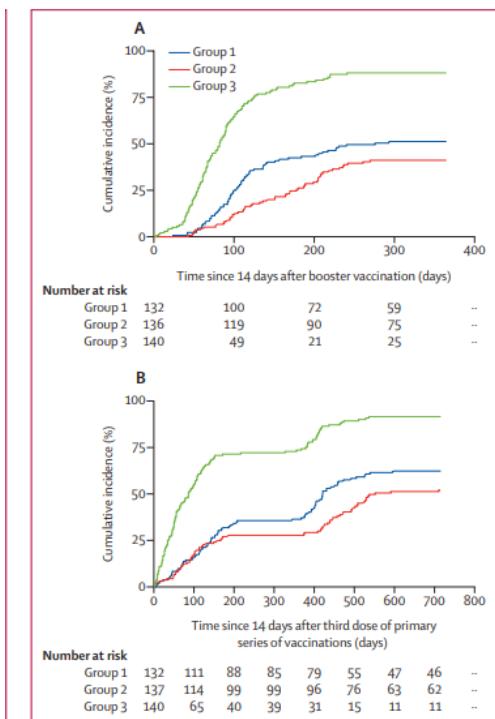


Figure 2: Kaplan-Meier estimates of the time to first episode of clinical malaria according to the primary case definition
The primary case definition of clinical malaria in this study was the presence of an axillary temperature of 37.5°C or greater and *Plasmodium falciparum* parasite density greater than 5000 asexual forms per µL. Analyses of vaccine efficacy included all participants who received a booster vaccination. (A) Data beginning from 14 days to 12 months after the booster vaccination. (B) Data beginning from 14 days to 24 months after the primary series of vaccinations. Group 1 received 5 µg R21/25 µg Matrix-M, group 2 received 5 µg R21/50 µg Matrix-M, and group 3, the control group, received the Rabivax-S rabies vaccine.

Mer på gång..

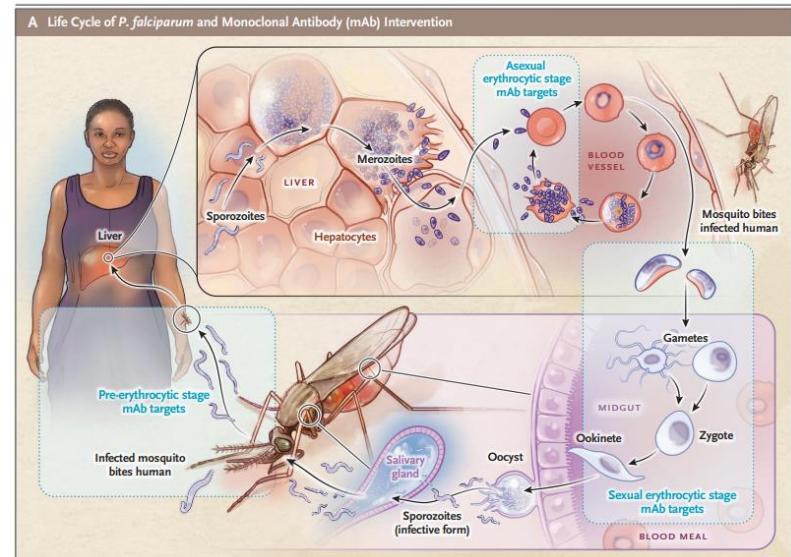
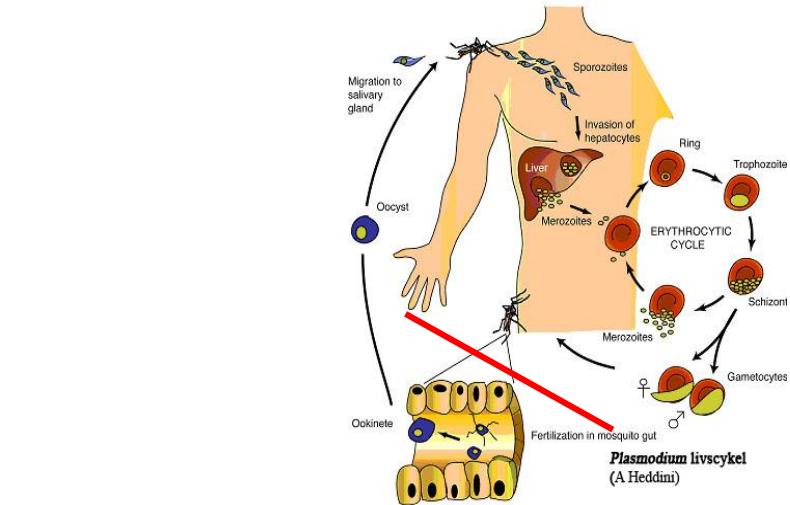
- Transmission blocking vaccines
- mRNA vaccine (BioNTech)
- Monoklonal antikroppar som förebyggande behandling
- P vivax vaccines

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OPEN Immunogenicity of a *Plasmodium vivax* vaccine based on the duffy binding protein formulated using adjuvants compatible for use in humans

Francisco J. Martinez¹, Micheline Guillotte-Blisnick¹, Christèle Huon¹, Patrick England², Jean Popovic³, Hélène Laude⁴, Laurence Arowas⁴, Marie-Noëlle Ungeheuer⁴, Jenny M. Reimer⁵, Derrick Carter^{6,7}, Steve Reed⁶, Paushali Mukherjee⁸, Virander S. Chauhan⁹ & Chetan E. Chitnis^{1,2,3}



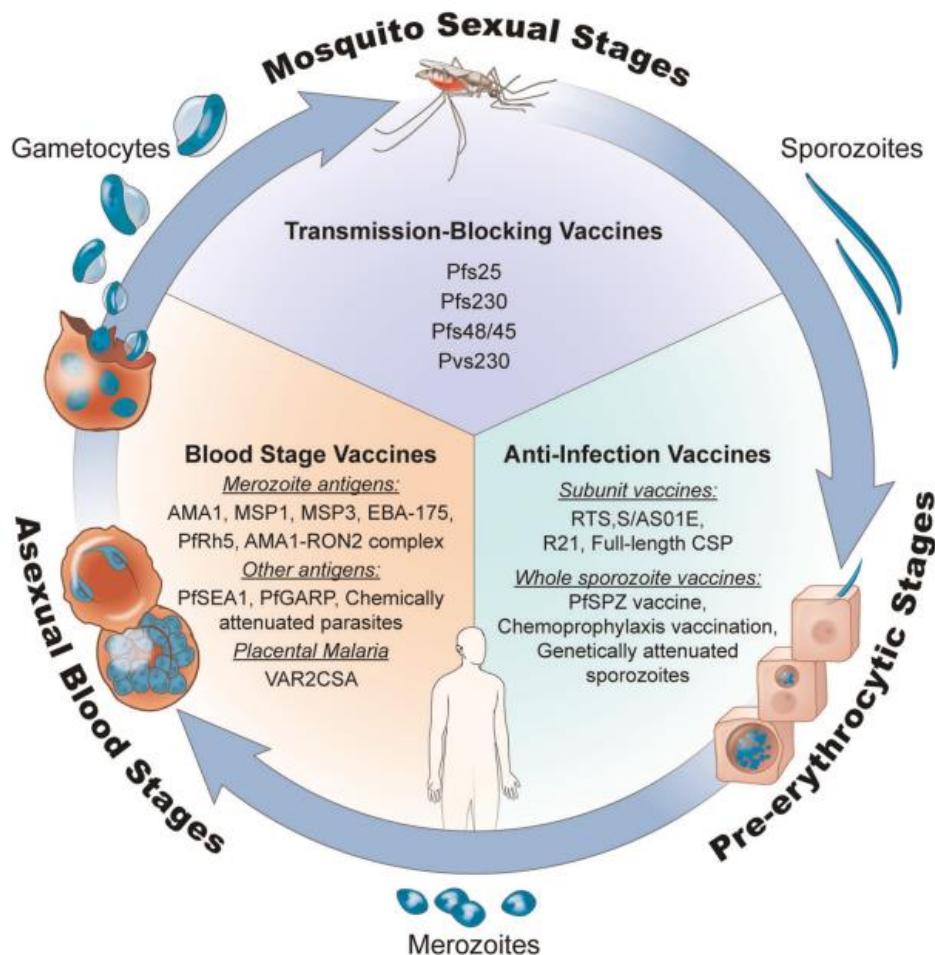


Fig. 1 Life cycle stages of *Plasmodium* and vaccine candidates that target each stage. This figure was adapted from a previously published illustration¹⁰⁵ that has been updated to include more recent malaria vaccine candidates. Illustration by Alan Hoofring, Medical Arts Design Section, NIH.

Tack!

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