

2019 Review and Update



AAFP GLOBAL HEALTH SUMMIT
Primary Health Care and Family Medicine: Health Equity for All

Malaria

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World Health Organization

'Malaria will not be eradicated in near future', warns WHO

Three-year review says new vaccines for eradicating disease are only 40% effective

Sarah Boseley Health editor
Thu 22 Aug 2018 20:25 EDT

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INCREASE STORAGE AND SECURITY

AMERICAN ACADEMY OF FAMILY PHYSICIANS

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Dr. Huntington has indicated he has no relevant financial relationships to disclose.

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HEALTH NEWS SEPTEMBER 8, 2018 / 5:37 PM / 3 DAYS AGO

Malaria can be eradicated by 2050, say global experts

Kate Kelland 4 MIN READ

LONDON, Sept 8 (Reuters) - Malaria can be eradicated within a generation, global health experts have said.



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Global Context

- Documented since 2700BC
- Asia to Africa then Europe
- Comes to Americas in 1500s
- Tropical *and temperate!*
- First seen in 1880
- 219 million cases in 2017 (up 3 million from the prior year)
- 435,000 deaths in 2017
- "Nearly eradicated" 1940s, 1980s, 2000s, etc.

www.who.int/news-room/fact-sheets/detail/malaria

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To stamp out the disease by 2050, the report's authors proposed three ways to speed up malaria's decline.

Existing malaria-fighting tools such as bednets, medicines and insecticides should be used more smartly, it said,

and new tools such as vaccines should be developed.

Thirdly, governments in both malaria-affected and malaria-free countries need to boost investment by about \$2 billion a year to accelerate progress.

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Cases

- ▶ 35 year old kayaker returns from Amazon adventure with fever (103°), headache, and malaise.
- ▶ 10 year old Rwandan girl treated at health outpost for fever (103°) and altered mentation develops renal failure.

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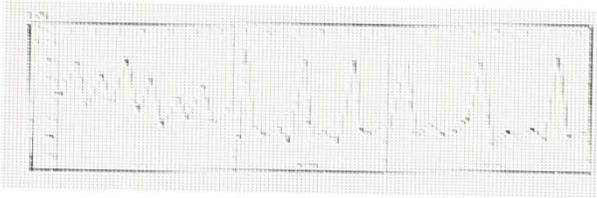
Clinical picture

- Cyclic fever
- Anemia
- Cerebral malaria

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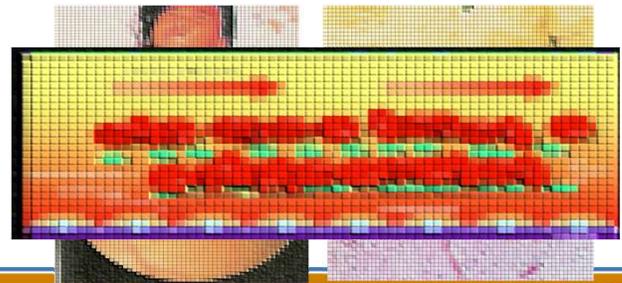
Clinical Picture

- Cyclic fever



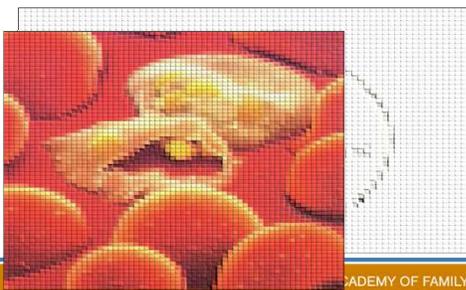
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Cerebral malaria



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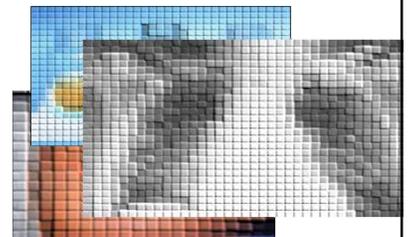
Schizogony



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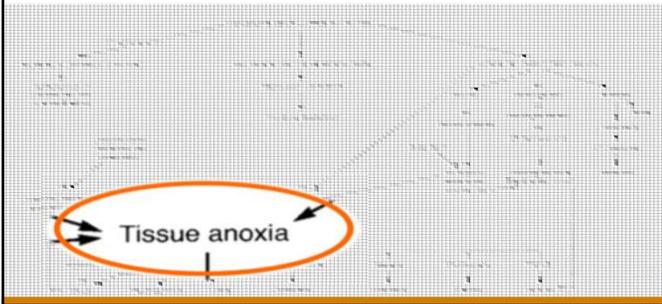
Clinical picture

- Cyclic fever
- Anemia
- Cerebral malaria
- Renal complications
- Pulmonary edema
- Diarrhea
- Splenic rupture
- Jaundice
- Hypoglycemia



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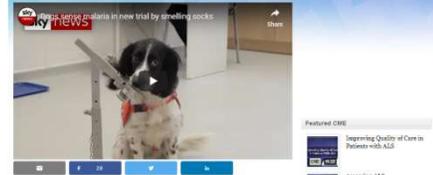
Pathophysiology



Emerging technologies

(not CAT scanning...)

Can Canines Identify Malaria-Infected Humans Before Symptom Onset?



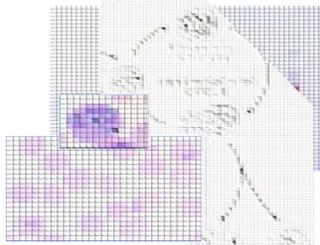
Dogs can be trained to help humans in any number of ways, from sniffing out explosives to comforting sick patients. Now, three dogs have learned to detect the deadly malaria parasite.

When researchers in Africa presented the dogs with 175 different box samples, the dogs detected malaria with 70 percent accuracy. The same canines had an even higher success rate in identifying malaria-positive samples. Researchers hope that one day the dog will be able to...

Diagnosis

Strategies

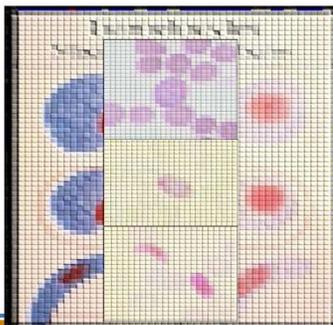
- Clinically?
- Antigen testing
- DNA testing
- Microscopy
 - trophozoites
 - gametes



Am J Trop Med Hyg. 2012;86:192

Drugs

- Chloroquine – standard; resistance
- Mefloquine – black box warning
- Malarone – daily for prophylaxis
- Quinine/quinidine – for treatment in Africa
- Coartem – Chinese herb
- Doxycycline – photosensitizing
- Primaquine/tafenoquine – hypnozoites

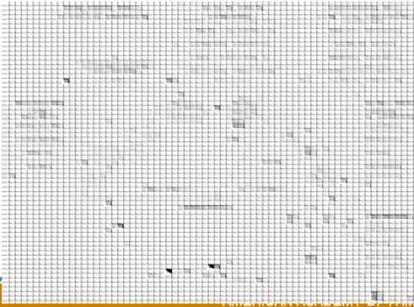


Intra-cellular Targets



J. Clin. Invest. 118(4): 1266-1276 (2008); <http://www.jci.org/articles/view/3366>

Stages targeted



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Transmission

- Via *Anopheles* bite
Based on bite frequency & infection intensity.
- Blood-borne
- Congenital

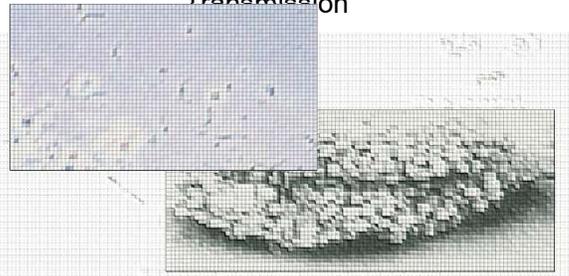
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Drugs

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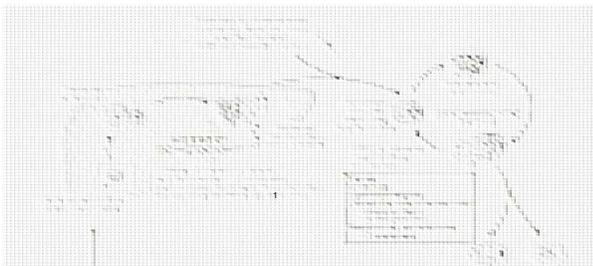
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Transmission



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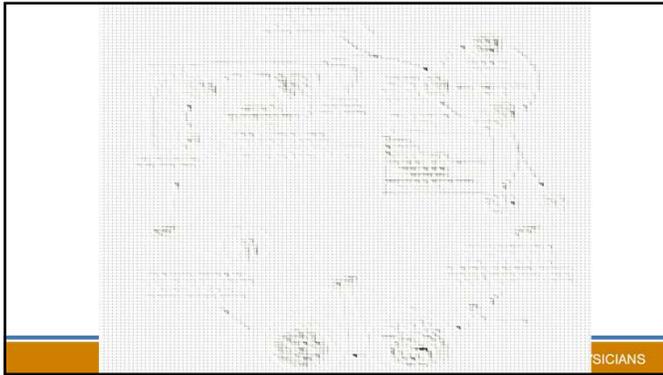
Hypnozoites



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The Big Picture

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Treat adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) with intravenous or intramuscular artesunate for at least 24 h and until they can tolerate oral medication. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of an ACT (add single dose primaquine in areas of low transmission).

Strong recommendation, high-quality evidence

Revised dose recommendation for parenteral artesunate in young children

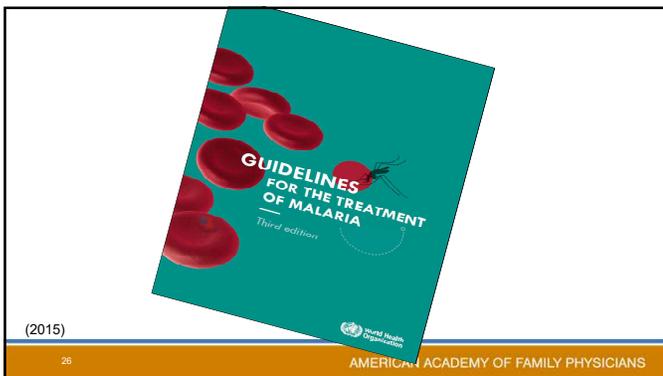
Children weighing < 20 kg should receive a higher dose of artesunate (3 mg/kg bw per dose) than larger children and adults (2.4 mg/kg bw per dose) to ensure equivalent exposure to the drug.

Strong recommendation based on pharmacokinetic modelling

Parenteral alternatives when artesunate is not available

If parenteral artesunate is not available, use artemether in preference to quinine for treating children and adults with severe malaria.

Conditional recommendation, low-quality evidence



(2015)

Artesunate: limited availability in US

Arlington, Va. (August 23, 2019) – Many ASTMH members are concerned about the lack of immediately available artesunate for U.S. clinicians caring for patients with severe malaria and the possible negative effect of lengthy transport times on patient outcomes when requesting artesunate from CDC.

ASTMH has been working with CDC and FDA for the past year on this troubling issue and sent a letter to the FDA in June 2019 addressing these concerns. The CDC and FDA are actively working together to facilitate the prompt availability of IV artesunate to patients with severe malaria. We look forward to both agencies providing additional information very soon.

Of note, La Jolla Pharmaceutical received orphan drug status... this development gives reason for hope that artesunate could be available in the United States in the near future.

Treatment

Treat children and adults with uncomplicated *P.falciparum* malaria (except pregnant women in their first trimester) with one of the following recommended ACTs:

- artemether + lumefantrine
- artesunate + amodiaquine
- artesunate + mefloquine
- dihydroartemisinin + piperazine
- artesunate + sulfadoxine-pyrimethamine (SP).

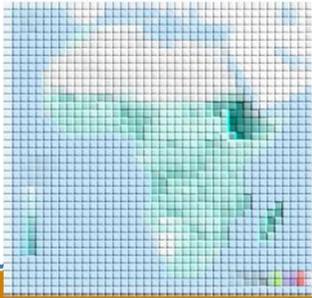
Strong recommendation, high-quality evidence

Duration of ACT treatment

ACT regimens should provide 3 days' treatment with an artemisinin derivative.



Vivax malaria is an increasing threat in Africa



PLoS Negl Trop Dis. 2019 Jan 31;13(1):e0007140

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Repellents & insecticides

Repellent	Concentration	Complete protection time
DEET	50%, 1g/limb (20-30%)	30 hours (up to 10 hours)
IR3535	20%	up to 10 hours
Picaridin	10-20%	up to 8 hours
Lemon eucalyptus*	30%	up to 12 hours

*distinct from essential oils of eucalyptus, which are ineffective

Travel Medicine and Infectious Disease 2013;11:374-411
Public Health Research and Practice 2016;26:e2651657

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Treatment

Relapsing malaria caused by *P. ovale*

- treated like vivax malaria

Malaria caused by *P. malariae*

- Treated like vivax malaria, only does not require primaquine (no hypnozoites in this species)

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Repellents & insecticides

DDT – historic, controversial but still potential value

Permethrin – applied to bednets and clothing, *not skin*

Ivermectin – xenointoxication (poisoned blood)

Med Vet Entomol. 2000 Dec;14(4):345-54
JMMR Res Protoc. 2016 Nov 17;3(4):e213
Angew Chem Int Ed Engl. 2017 Jul;16(14):4067-71. doi: 10.1002/anie.201704077.
Trends Parasitol. 2017 May 9; pii: S1471-4922(17)30107-1. doi: 10.1016/j.pt.2017.04.006.

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Control & prevention

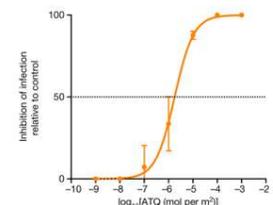
- A – **A**wareness
- B – **B**ed nets/ **B**arriers/ **B**ug repellants
- C – **C**hemoprophylaxis
- D – rapid **D**iagnosis and treatment

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New approach to bednets?

- Impregnation with antimalarial rather than insecticide?
- Kill the parasite, not the vector
- Proof-of concept is promising



Nature 2019;567:239

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Vaccination?

~50 projects reached clinical stage

- Only pre-erythrocyte stage-based reduce morbidity
- Use *multiple-episodes* to assess
- *In vitro* or animal studies ≠ field efficacy



Malaria Journal 2012, 11:11 doi:10.1186/1475-2875-11-11

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Issued: Thursday, 30 June 2016

FEBS Journal
MINIREVIEW

FEBS PRESS
The world's leading life sciences journal

Vaccines against malaria—still a long way to go

Kai Matuschewski

Department of Molecular Parasitology, Institute of Biology, Humboldt University Berlin, Germany

Keywords:
geneticotype; immunization; malaria; macrozoite; Plasmodium falciparum; Plasmodium vivax; sporozoite; vaccine

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(Received 31 January 2017, revised 9 April 2017, accepted 10 May 2017)

Several species of *Plasmodium* cause a broad spectrum of human disease that range from nausea and fever to severe anemia, cerebral malaria, and multiorgan failure. In malaria-endemic countries, continuous exposure to *Plasmodium* sporozoite inoculations and subsequent blood infections elicit only partial and short-lived immunity, which gradually develops over many years of parasite exposure and multiple clinical episodes. The ambitious goal of malaria vaccinology over the past 70 years has been to develop an immunization strategy that mounts protection superior to naturally acquired immunity. Herein, three principal concepts in evidence-based malaria vaccine development are compared. Feasible leads are typically stand-alone subunit vaccine approaches that block *Plasmodium* parasite life cycle progression or parasite/host interactions, and they constitute the majority of candidates in preclinical research and early clinical testing. Integrated approaches incorporate malaria antigen(s) into licensed or emerging pediatric vaccine formulations. This strategy can complement the

Produce a standard national out

36364

SIANS

Issued: Thursday 24 July 2014, London UK

GSK announced today that it has submitted a regulatory application to the European Medicines Agency for its malaria vaccine candidate, RTS,S

The submission will follow the Article 58 procedure, which allows the EMA to assess the quality, safety and efficacy of a candidate vaccine, or medicine, manufactured in a European Union (EU) member state, for a disease recognised by the World Health Organization (WHO) as of major public health interest, but intended exclusively for use outside the EU.

RTS,S is intended exclusively for use against the *Plasmodium falciparum* malaria parasite, which is most prevalent in sub-Saharan Africa (SSA). Around 90 per cent of estimated deaths from malaria occur in SSA, and 77 per cent of these are in children under the age of 5.

Fortune.com

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The Maravi Post

The world's first vaccine against malaria will be introduced in three countries – Ghana, Kenya and Malawi – starting in 2018.

...but it is not yet clear if it will be feasible to use in the poorest parts of the world. The vaccine needs to be given **four** times – once a month for three months and then a fourth dose 18 months later.

(12 Sep 2017)

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Issued: Friday 24 July 2015

The European Medicines Agency in London declared Mosquirix safe for use and moderately effective against the malaria parasite, *Plasmodium falciparum*, in combination with established protective measures such as bednets. The World Health Organization must now formally agree to recommend its use in children. ...[Mosquirix] is also protective against hepatitis B.

Nature 2015;523:507

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Malawi's Malaria Vaccine Programme on track

By Author / Wednesday, 04 Sep 2019 05:42AM / Leave a Comment / Tags: Malawi's Malaria Vaccine Programme on track / 219 views

By John Saukira

LILONGWE (MaraviPost) - Malaria Vaccine Implementation Programme (MVIP) which Government rolled out in 11 districts in **April this year** has started bearing fruits.

www.maravipost.com

(Ghana began on 30 April 2019, too)

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HEALTH NEWS | OCTOBER 13, 2018 | 1:09 AM / UPDATED AN HOUR AGO

Kenya becomes third African nation to introduce malaria vaccine

3 MIN READ

NAIROBI (Reuters) - Kenya on Friday began adding a malaria vaccine to its routine immunization schedule for babies and toddlers, becoming the third African country to roll out the vaccine for a disease that threatens children across the continent.

Malaria, which kills one child globally every two minutes, is the top killer of children under five in the east African country. The vaccine - the world's first against malaria - will be administered to children under two and could be crucial to efforts to combat the disease, health officials said.

Other measures, such as nets to protect people from the mosquitoes that carry the malaria parasite, have not proven adequate to halt transmission, the director general of

Drug resistance

	Low transmission	High transmission
C	32%	68%
D	3%	97%

So...
As we **reduce transmission**, be prepared for **increased drug resistance**!?

single mixed single mixed

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New vaccine candidates for malaria

July 6, 2018

Gates Foundation Funds Research For New Synthetic Malaria Vaccine

Yale study raises hope of vaccine

Novel Malaria Vaccine Shows Activity Only at Peak Titers

Malaria vaccine targets PMIF

A malaria transmission-blocking vaccine, Ph2D4-EPA in AlysioGel[®], was well tolerated and safe and induced significant blockage of parasite transmission, but this activity was only seen at peak titer after 4 vaccine doses, according to a report published in The Lancet Infectious Diseases.

Ph2D4-EPA is a protein-protein conjugate transmission-blocking vaccine against Plasmodium falciparum and has demonstrated safety and the ability to induce antibodies in malaria-naïve individuals. This study assessed the vaccine for safety and functional immunogenicity in malaria-exposed adults residing in Mali. An initial pilot safety assessment was conducted, followed by a main phase 1 trial. Participants (10 in each arm) in the pilot cohort received 2 doses of Ph2D4-EPA in AlysioGel 16 µg or Euvax B as a comparator, while participants in the main phase 1 (50 in each arm) received Ph2D4-EPA in AlysioGel 47 µg or comparator vaccine (Euvax B for vaccines 1-3 and Menaxx[®] for vaccine 4).

A malaria vaccine has been created that protects against malaria in mouse models, researchers have just announced. This opens the door towards a human vaccine which targets the parasite's life cycle of malaria parasites.

Yale researchers have a vaccine, focusing on preventing malaria from spreading to humans.

Yale researchers have a vaccine, focusing on preventing malaria from spreading to humans.

Questions & discussion

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• Interaction with *Ascaris* seem

"Ascaris lumbricoides and Trichuris trichiura were both associated with direct reductions in cerebral malariahalved in the presence of hookworm"

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