Malaria

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No child should die from malaria...And the only way to end death from malaria is to end malaria.

Any goal short of eradicating malaria is accepting malaria; it’s making peace with malaria; it’s rich countries saying: ‘We don’t need to eradicate malaria around the world as long as we’ve eliminated malaria in our own countries.’ That’s just unacceptable.

Did They Really Say ... Eradication?

The malaria world is all abuzz about a call by Bill and Melinda Gates to wipe the scourge from the planet. Even if it proves unfeasible, their idea could have a big impact.
Right now, we’re on track to end the scourge of HIV/AIDS. That’s within our grasp. And we have the chance to accomplish the same thing with malaria. Something I’ll be pushing this Congress to fund this year.
Welcome to your preview of The Times

George Osborne in £3 billion vow with Bill Gates to beat malaria
Malaria: a complex disease

- No symptoms
- Fever
- Rigors
- Myalgia
- Headache

1-3%

Severe Disease

10-15%

Death

NIAID
What is needed for eradication?

1. Vector control
   Prevent mosquito from acquiring or passing on an infection (ITN or IRS)

2. Chemoprevention
   Suppress and prevent infections establishing themselves in human beings

3. Case management
   Detect, diagnose, treat and cure infections

World Malaria Report 2015, WHO
Signs of progress

Figure 2.1 Estimated malaria case incidence and death rate globally, 2000–2015

Source: WHO estimates

World Malaria Report 2015, WHO
Fewer child deaths

Figure 2.4 Leading causes of death among children aged under 5 years in sub-Saharan Africa, 2000–2015

Conditions that are responsible for more than 10 deaths per 1000 live births during any time between 2000 and 2015 are shown.

Source: WHO estimates

World Malaria Report 2015, WHO
Figure 2.5 Estimated \( P. \) falciparum infection prevalence among children aged 2–10 years (\( PfPR_{2-10} \)) in 2000 and 2015.

Figure 3.1 Proportion of population at risk with access to an ITN and proportion sleeping under an ITN, sub-Saharan Africa, 2000–2015.

Figure 3.18 Predicted time series of \( PfPR_{2-10} \) across endemic Africa with and without interventions, 2000–2015.

API, annual parasite index; \( PfPR \), \( P. \) falciparum parasite rate

Source: Malaria Atlas Project (18)
Measurements of success

**Figure 3.19 Predicted cumulative number of malaria cases averted by interventions, sub-Saharan Africa, 2000–2015**

- Cases averted due to ITNs
- Cases averted due to ACTs
- Cases averted due to IRS
- Total averted not attributable to IRS, ITNs, or ACTs

ACT, artemisinin-based combination therapy; IRS, indoor residual spraying; ITN, insecticide-treated mosquito net. Source: *Malaria Atlas Project (18) estimates of cases averted attributable to ITNs, ACTs, and IRS and WHO estimates of total cases averted*
Four years of high coverage malaria control interventions on Bioko Island: Under-5 mortality fell from 152 per 1,000 births to 55 per 1,000 births.
Artesunate for severe malaria

AQUAMAT Dondorp et al. Lancet 2010
Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial

RTS,S Clinical Trials Partnership*
Efficacy in 5-17m old children

A Clinical malaria, R3C group

- Kilifi, Kenya: 66.0 (37.5-81.5)
- Korogwe, Tanzania: 52.0 (26.2-68.8)
- Manhiça, Mozambique: 33.3 (7.1-52.1)
- Lambaréné, Gabon: 36.1 (10.8-54.1)
- Bagamoyo, Tanzania: 37.5 (13.5-54.9)
- Lilongwe, Malawi: 33.5 (8.2-51.8)
- Agogo, Ghana: 31.1 (13.4-45.2)
- Kombewa, Kenya: 27.1 (12.9-38.9)
- Kintampo, Ghana: 25.9 (15.0-35.4)
- Nanoro, Burkina Faso: 17.7 (7.0-27.2)
- Siaya, Kenya: 20.2 (7.4-31.3)
- Overall: 28.2 (23.3-32.9)

No Booster dose

B Clinical malaria, R3R group

- Kilifi, Kenya: 74.6 (47.8-87.6)
- Korogwe, Tanzania: 46.8 (18.4-65.3)
- Manhiça, Mozambique: 22.0 (-6.6 to 42.9)
- Lambaréné, Gabon: 41.1 (15.3-59.0)
- Bagamoyo, Tanzania: 37.9 (12.8-55.8)
- Lilongwe, Malawi: 50.8 (31.4-64.7)
- Agogo, Ghana: 43.2 (29.0-54.6)
- Kombewa, Kenya: 32.1 (18.9-43.2)
- Kintampo, Ghana: 35.0 (25.5-43.4)
- Nanoro, Burkina Faso: 27.9 (17.9-36.8)
- Siaya, Kenya: 37.8 (26.6-47.2)
- Overall: 36.3 (31.8-40.5)

Booster dose

C Severe malaria, R3C group

- Kilifi, Kenya: 100.0 (-3800 to 100.0)
- Korogwe, Tanzania: 83.4 (-36.9 to 99.6)
- Manhiça, Mozambique: 77.7 (-139.3 to 64.9)
- Lambaréné, Gabon: 61.7 (-14.5 to 89.3)
- Bagamoyo, Tanzania: 45.4 (-81.5 to 85.6)
- Lilongwe, Malawi: -8.7 (-223.9 to 62.8)
- Agogo, Ghana: -21.4 (-166.1 to 43.7)
- Kombewa, Kenya: -27.6 (-131.0 to 28.7)
- Kintampo, Ghana: -48.4 (-142.1 to 70.9)
- Nanoro, Burkina Faso: -13.0 (-182.6 to 54.4)
- Siaya, Kenya: 19.9 (-27.8 to 50.1)
- Overall: 1.1 (-23.0 to 20.5)

D Severe malaria, R3R group

- Kilifi, Kenya: -3.1 (-79.9 to 98.7)
- Korogwe, Tanzania: 66.6 (-87.0 to 96.7)
- Manhiça, Mozambique: 62.9 (-25.3 to 91.4)
- Lambaréné, Gabon: 77.0 (16.4 to 95.8)
- Bagamoyo, Tanzania: 78.1 (-5.9 to 97.7)
- Lilongwe, Malawi: 39.4 (-110.2 to 84.4)
- Agogo, Ghana: 50.0 (-32.4 to 82.9)
- Kombewa, Kenya: 36.3 (-27.4 to 69.4)
- Kintampo, Ghana: -19.4 (-98.9 to 27.9)
- Nanoro, Burkina Faso: 17.4 (-119.3 to 69.7)
- Siaya, Kenya: 28.7 (-15.4 to 56.5)
- Overall: 32.2 (13.7 to 46.9)

Lancet 2015
Efficacy in 6-12 week infants

No Booster dose

Booster dose

Lancet 2015
## Efficacy over time

<table>
<thead>
<tr>
<th>5-17 months age category</th>
<th>C3C group</th>
<th>R3C group</th>
<th>R3R group</th>
<th>Point estimate of VE unadjusted for covariates R3C vs C3C</th>
<th>Point estimate of VE unadjusted for covariates R3R vs C3C</th>
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<tr>
<td></td>
<td>N</td>
<td>n</td>
<td>Proportion affected*</td>
<td>N</td>
<td>n</td>
</tr>
<tr>
<td>Month 0 to study end</td>
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<td>171</td>
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<td>2972</td>
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<tr>
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<td>152</td>
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<td>Months 0-20†</td>
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<td>0.04</td>
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<td>Months 21-32</td>
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<td>0.02</td>
<td>2719</td>
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</tbody>
</table>

### Analyses

Analyses were modified by intention to treat. p values were calculated using a two-sided Fisher’s exact test. C3C=control group. N=number of participants. n=number of participants with at least one event in each group. R3C=RTS,S/AS01 primary schedule without booster. R3R=RTS,S/AS01 primary schedule with booster. VE=vaccine efficacy (1-relative risk for severe malaria). *Proportion of participants who reported at least one event. Data from a previous analysis that compared R3R with R3C with C3C.

### Table 2: Efficacy against severe malaria (primary case definition) of a primary schedule with or without a booster dose

Lancet 2015
Insecticide resistance

Figure 5.16 Reported pyrethroid resistance status of malaria vectors, measured with insecticide bioassays since 2010

Data shown are for standard bioassays. Where multiple insecticide classes or types, mosquito species or time points were tested, the highest resistance status is shown.

Source: National malaria control programme reports, African Network for Vector Resistance, Malaria Atlas Project, President’s Malaria Initiative (United States), scientific publications.
Antimalarial resistance

Spread of Artemisinin Resistance in *Plasmodium falciparum* Malaria

E.A. Ashley, M. Dhorda, R.M. Fairhurst, C. Amaratunga, P. Lim, S. Suon, S. Sreng, L. Lee, N. Molyneux, N. White

*The New England Journal of Medicine*

Ashley, NEJM 2014
Vaccine resistance

B Circumsporozoite Protein
Length = 397 aa

C Cumulative Vaccine Efficacy over Time
- Vaccine efficacy against 3D7 match
- Vaccine efficacy against 3D7 mismatch
- 95% Confidence interval

Days since 14 Days after Vaccine Dose 3

Neafsey, NEJM 2015
Loss of immunity and severe malaria

Changing Trends in *P. falciparum* Burden, Immunity, and Disease in Pregnancy

Alfredo Mayor, Ph.D., Azucena Bardaji, Ph.D., Eusebio Macete, Ph.D., Tacita Nhampossa, Ph.D., Ana Maria Fonseca, M.Sc., Raquel González, Ph.D., Sonia Maculuve, M.D., Pau Cisteró, M.Sc., Maria Rupérez, M.D., Joe Campo, Ph.D., Anifa Vala, D.V.M., Betuel Sigaúque, Ph.D., Alfons Jiménez, M.Sc., Sonia Machave, M.D., Laura de la Fuente, B.Sc., Abel Nhama, M.D., Leopoldina Luis, B.Sc., John J. Aponte, Ph.D., Sozinho Acáio, M.D., Arsenio Nhacolo, B.Sc., Chetan Chitnis, Ph.D., Carlota Dobaño, Ph.D., Esperanza Severa, Ph.D., Pedro Luis Alonso, Ph.D., and Clara Menéndez, Ph.D.

**CONCLUSIONS**

Antimalarial antibodies were reduced and the adverse consequences of *P. falciparum* infections were increased in pregnant women after 5 years of a decline in the prevalence of malaria. (Funded by Malaria Eradication Scientific Alliance and others.)
Severe *P. falciparum* malaria in children: syndromes and mortality

Cunnington et al. Science Translational Medicine 2013
The Puzzle of Severe Malaria

Cunnington et al. Science Translational Medicine 2013
Host-pathogen interactions – systemic to molecular

Cunnington et al. Science Translational Medicine 2013
Modelling host-pathogen interaction in humans

**Observed:**

- Number of new pRBCs/cycle
- Number of replication cycles
- Killing of parasites by host response
- Parasite density/biomass

**Unobserved:**

- Variation between individuals

*Variation between individuals*
How can we estimate within-host dynamics in humans?

Problem:
- We usually only have measurements at one point in time
  - Unethical to delay treatment just to make serial measurements

Possible solution:
- Make a “reference map” of the dynamic course of untreated infection
- Triangulate position using the measurements we can make
First wave of parasitemia in malariatherapy patients

- Parasite density
- Time since infection
- Onset of fever
Estimation of unmeasurable components (latent variables) in Gambian children
Filling in the gaps in the puzzle: transcriptomic approach

Identifying differences in **simultaneous** host and parasite gene expression **between** discrete severe malaria syndromes

Adapted from Westermann et al. Nat Rev Microbiol. 2012
• ~35 million reads of 100 base pair length, per subject
• 92 % can be uniquely assigned to a single position in human or parasite genome
• ~20,000 human and ~4500 parasite genes detected
Every human cell type and parasite stage has its own transcriptional signature.

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Bozdech et al. Plos Biology 2003
Questions we can address with this approach

- Which host molecules kill parasites
- What controls parasite growth rate
- What host factors cause severe malaria
- What parasite factors cause severe malaria
- What triggers gametocytogenesis

- Potential therapy / vaccine strategy
- Therapeutic target
- Adjunctive therapy
- Vaccine targets / adjunctive therapy
- Transmission blockade
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Athina Georgiadou
Clive Hoggart
Michael Bretscher
Azra Ghani

LSHTM
Eleanor Riley
David Conway
Julius Haffalla

IMB Brisbane
Lachlan Coin
Hyun Jae Lee

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Madi Njie, Lamin Manneh
Michael Walther

Jammeh Foundation Hospital
Brikama Health Centre
MRC Clinic
Clinical, Lab and Field Staff
The Study Subjects

Exeter University
Konrad Paskiewicz

University of Tübingen
Prof Klaus Dietz