Global Health aspects of Malaria 2019

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J.D. MacLean Centre for Tropical Diseases
McGill University Health Centre
I have received in-kind research support from *BD Molecular Diagnostics* and *bioMerieux* for work on enteric infections in the Arctic.
Learning objectives

1. Understand the burden of malaria disease
2. Be familiar with key clinical and biological aspects of human malaria
3. **Know the main tools used for malaria control programs**
4. Know how malaria burden can be measured
5. **Understand trends in global malaria epidemiology**
6. **Understand key barriers to malaria control (and elimination)**
Outline

1. Some history and biology
2. Disease in individuals
3. Tool for malaria control
4. Where are we at in 2019?
5. Urgent threats to control (and elimination)
6. Endgame thought (?)
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Some history and biology

malaria basics

Yangon, Myanmar; ca. 1986
Some history and biology

*malaria basics*

- Parasite of human RBCs
- THE parasitic killer of human beings
  - 700,000 – 1.1 million deaths/year (>2000/day)
  - 216 million cases in 2010
- 90% of deaths in sub-Saharan Africa
- Transmitted by *Anopheles* mosquitoes
Put another way:

Scorpion
3,200

Sandfly
>60,000

Tick
(?)
Anopheles mosquito – eg MALARIA

Life-cycle

Lancet 2014; 383: 723–35
Some history and biology

the vector

- *Plasmodium falciparum*
- *Plasmodium vivax*
- *Plasmodium ovale*
- *Plasmodium malariae*
- *Plasmodium knowlesi*
Some history and biology

*the vector*

- Bite dusk to dawn
- Only females
- Inactive below 18°
- Altitude sensitive
- **DEET** and **picaridin** are the ONLY effective repellents
- Permethrin-treated clothes/nets/curtains
- Don’t like cities*
Some history and biology

global map of dominant malaria vectors
Some history and biology

where falciparum malaria occurred in 19th C
Some history and biology

*where* falciparum *malaria* *occurs now*
Some history and biology

where vivax malaria occurs
Some history and biology

*malaria is an old nemesis of humans*

“Malaria is the strongest known force for evolutionary selection in the recent history of the human genome”


**REVIEW ARTICLE**
How Malaria Has Affected the Human Genome and What Human Genetics Can Teach Us about Malaria

Dominic P. Kwiatkowski

Wellcome Trust Centre for Human Genetics and University Department of Paediatrics, Oxford, United Kingdom
Some history and biology: Malaria is an old nemesis of humans. For example, Thalassemia protects against severe malaria but appears to enhance mild malaria episodes in some environments. HBs and HBC alleles protect against severe malaria. HBE alleles reduce parasite invasion.

### Table 1: Host Molecules Mediated Cytoadherence by P. falciparum-Infected Erythrocytes and That Have Been Reported to Show Association with Resistance or Susceptibility to Malaria

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Function</th>
<th>Reported Genetic Associations with Malaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD36</td>
<td>CD36 antigen, thrombospondin receptor</td>
<td>PE-binding receptor on endothelium and dendritic cells</td>
<td>CD36 polymorphisms show variable associations with severe malaria in the Gambia, Kenya, and Thailand.</td>
</tr>
<tr>
<td>CR1</td>
<td>CR1, complement receptor 1</td>
<td>PE-binding receptor on erythrocytes</td>
<td>CR1 polymorphisms show variable associations with severe malaria in the Gambia, Thailand, and Papua New Guinea.</td>
</tr>
<tr>
<td>ICAM1</td>
<td>ICAM1, intercellular adhesion molecule-1</td>
<td>PE-binding receptor on endothelium</td>
<td>ICAM1 polymorphisms show variable associations with severe malaria in Kenya, Gabon, and the Gambia.</td>
</tr>
<tr>
<td>PECAM1</td>
<td>PECAM1, platelet-endothelial cell-adhesion molecule</td>
<td>PE-binding receptor on endothelium</td>
<td>PECAM1 polymorphisms show variable associations with severe malaria in Thailand, Kenya, and Papua New Guinea.</td>
</tr>
</tbody>
</table>

* PE = parasitized erythrocyte.

### Table 2: Immune Genes Reported to Be Associated with Different Malaria Phenotypes

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<th>Protein</th>
<th>Function</th>
<th>Reported Genetic Associations with Malaria</th>
</tr>
</thead>
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<tr>
<td>FCGR2A</td>
<td>CD32, low affinity receptor for Fc fragment of IgG</td>
<td>Clearance of antigen-antibody complexes</td>
<td>Association with severe malaria in the Gambia.</td>
</tr>
<tr>
<td>HLA-B</td>
<td>HLA-B, a component of MHC class I</td>
<td>Antigen presentation that leads to cytotoxic T cells</td>
<td>HLA-B53 association with severe malaria in the Gambia.</td>
</tr>
<tr>
<td>HLA-DR</td>
<td>HLA-DR, a component of MHC class II</td>
<td>Antigen presentation that leads to antibody production</td>
<td>HLA-DRB1 association with severe malaria in the Gambia.</td>
</tr>
<tr>
<td>IFNAR</td>
<td>Interferon receptor component</td>
<td>Cytokine receptor</td>
<td>Association with severe malaria in the Gambia.</td>
</tr>
<tr>
<td>IFNG</td>
<td>Interferon-γ receptor</td>
<td>Cytokine receptor</td>
<td>Weak associations with severe malaria in the Gambia.</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor necrosis factor</td>
<td>Cytokine with antiparasitic and proinflammatory properties</td>
<td>Haploident familial association with severe malaria in Tanzania.</td>
</tr>
<tr>
<td>CD40L</td>
<td>CD40 ligand</td>
<td>T cell-B cell interactions leading to immunoglobulin class switching</td>
<td>Association with severe malaria in the Gambia.</td>
</tr>
</tbody>
</table>
Outline

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2. **Disease in individuals**
3. Tool for malaria control
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6. Endgame thought (?)
Severe malaria: new insights

(P. vivax)

(P. knowlesi)

(P. vivax)

(P. malariae)

(P. ovale)

rendent malade
mais ne tuent pas

P. falciparum

peut tuer (accès
pernicieux)
Physiopathology severe malaria: *P. falciparum*

- Severe hemolysis
Severe malaria: hemolysis

- Anemia
- Jaundice
- Splenomegaly
- Thrombocytopenia (bleeding)
- Acute tubular necrosis
Physiopathology severe malaria: *P. falciparum*

- Severe hemolysis
- Sequestration
**Representation of blood flow through microchannel**

Although 8 μm in width, normal, uninfected erythrocytes are flexible enough to pass through central constriction of 2 μm diameter. By contrast, when infected with *P falciparum*, erythrocytes become spheroid and decreasingly deformable, such that, as shown, they block 6 μm constriction.

THE LANCET • Vol 363 • May 22, 2004 • www.thelancet.com
Sequestration: cerebral malaria

- Most important cause of death
- Obstruction microcirculation in brain
  - confusion, stupor, coma
  - convulsions
  - retina bleeding: bad prognosis
  - no neck stiffness, normal cerebrospinal fluid
  - 5-10% neurological sequellae
Sequestration: ARDS

Fig. 13. Acute pulmonary oedema developing immediately after delivery in a patient.

Plate 11 Chest retraction (recession of the intercostal spaces) in a Kenyan child with respiratory distress associated with metabolic acidosis in severe malaria. (Copyright DA Warrell.) See page 212.
ARDS in *P. falciparum* malaria   Day 1 to 5
Sequestration: end-organ failure
Physiopathology severe malaria: *P. falciparum*

- Severe hemolysis
- Sequestration
- Sepsis

Severe malaria DIC
Severe malaria: Black water fever

5% RBC parasitized by *P. falciparum*

G6PD 28 days later was very low.
Disease in individuals

complications according to age and endemicity

Fig. 1. The clinical presentations of severe falciparum malaria by age and transmission intensity. Nonimmune travelers are expected to behave like inhabitants of a zone of unstable transmission. (From White NJ. Malaria. In: Cook GC, Zumla AI, editors. Manson’s tropical diseases. 22nd edition. Philadelphia: Saunders Ltd; 2009. p. 1205; with permission.)
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Disease in individuals
*malaria-HIV interactions*

“Where 2 elephants meet, there grows no grass“
African proverb
Impact of HIV on malaria: summary

<table>
<thead>
<tr>
<th>HIV (low CD4 count) → Malaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasitemia</td>
</tr>
<tr>
<td>Clinical malaria</td>
</tr>
<tr>
<td>Severe Malaria</td>
</tr>
<tr>
<td>Antimalarial drug use</td>
</tr>
<tr>
<td>Treatment efficacy</td>
</tr>
<tr>
<td>Hemoglobin levels</td>
</tr>
</tbody>
</table>
Impact of malaria on HIV: summary

Malaria → HIV

<table>
<thead>
<tr>
<th>Specificity HIV RDTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient viral load</td>
</tr>
<tr>
<td>Transient CD4</td>
</tr>
</tbody>
</table>
| Progression to AIDS  | ?  
| HIV transmission     | (high HIV prevalence) |
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Tools for malaria community-level control

CONSULTATION MISSION
(split into groups of 4-6):

1. Determine **5 methods of malaria control** you would propose to national programmes

2. Rank them in order of priority

3. What impact do you expect?

(10 minutes)
Tools for malaria community-level control

**BITE PREVENTION:**
- Bednets*
- Repellents
- Clothing

**VACCINE**

**SUPPRESSIVE TREATMENT:**
- disease
- targeted Px
  - pregnancy
  - Infants?

**VECTOR REDUCTION:**
- I.R.S.
- Others…

Wait a minute, WHO do we treat?
- Passive detection?
- Active case-finding?
- Mass Rx (MDA)?
I myself have been infected with malaria only once in spite of nineteen years service in India and thirteen subsequent malaria expeditions to warm climates; I attribute this good fortune to my scrupulous use of the bed net.
**Prevention**

*repellent chemicals*

- Important for MANY diseases and discomfort
  - Malaria, dengue, WNV, many others!

- **Effective products:**
  - DEET (use 35-50% solutions)
  - Picardin (use 20% solution, only 7% available is US)*
  - Permethrin on clothes and bednets

- **Much less effective:**
  - Eucalyptus oil, 2% soybean oil

- **Not effective:**
  - Citronella, ultrasonic devices, ankle/wristbands, geranium oil, baby oil


Medical Letter Vol 47 (Issue 1210) June 6, 2005 “Deet alternatives”
Prevention

wear this

7up “Uncola” ad campaign
Prevention
don’t wear this
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Where are we at in 2019?

• Chloroquine resistance emerged in 1970s and reversed much of the gains made in Africa over the 20th Century
• Drastic increase in deaths and drug-resistant malaria 1970-2000
• MDGs and other initiatives in 2000 prompted concerted effort for control
Where are we at in 2019?

The effect of malaria control on *Plasmodium falciparum* in Africa between 2000 and 2015


Mapping *Plasmodium falciparum* Mortality in Africa between 1990 and 2015

This article was published on October 10, 2016, and updated on October 20, 2016, at NEJM.org.

DOI: 10.1056/NEJMoA1606701
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Where are we at in 2019?
Where are we at in 2019?
Where are we in 2019?

• This is not the comparative efficacy of each measure!

• Reflects
  • coverage
  • time since implementation
  • Local epidemiology, age structure, and ecology
Figure 2: Regional distribution of *Plasmodium falciparum*
To show trends across regions with such different endemic incidence (per 1000 individuals) for A and count (in million) via the corresponding coloured bands behind the mean line endemic countries within each region.

Figure 3: Spatial distribution of age-standardised *P falciparum* parasite rate (per 1000) in 2005 (top) and 2017 (bottom)
Note the colour scaling is split to better differentiate within low endemic areas, with one linear scale between zero and 0.01 *P falciparum* parasite rate (grey shades) and a second linear scale between 0.01 and 1 (colours from blue to red). Areas without endemic *P falciparum* are shown in white. *P falciparum* parasite rate, parasite rate for children aged 2-10 years of age.
Where are we at in 2019?

(Vivax:)

*Figure 2: Predicted incidence of *Plasmodium vivax* malaria in 2005 and 2017. Incidence in cases per 1000 people per year are shown on a spectrum of white (zero incidence) to dark grey (1 case per 1000) and then blue to red (>1 case per 1000 to >600 cases per 1000) for the years 2005 (top panel) and 2017 (bottom).*
Q: what does this mean for front line clinicians facing an ill febrile child?

Q: Does ↓malaria transmission ↑ or ↓ need for diagnostic tools?
Where are we in 2019? post-Ebola syndrome

Effects of Response to 2014–2015 Ebola Outbreak on Deaths from Malaria, HIV/AIDS, and Tuberculosis, West Africa

Alyssa S. Parpia,† Martel L. Ndeffo-Mbah,† Natasha S. Wenzel, Alison P. Galvani

Response to the 2014–2015 Ebola outbreak in West Africa overwhelmed the healthcare systems of Guinea, Liberia, and Sierra Leone, reducing access to health services for diagnosis and treatment for the major diseases that are endemic to the region: malaria, HIV/AIDS, and tuberculosis. To estimate the repercussions of the Ebola outbreak on the populations at risk for these diseases, we developed computational models for disease transmission and infection progression. We estimated that a 50% reduction in access to healthcare services during the Ebola outbreak exacerbat-ed malaria, HIV/AIDS, and tuberculosis mortality rates by additional death counts of 6,269 (2,564–14,407) in Guinea, 1,535 (522–2,878) in Liberia, and 2,819 (844–4,844) in Sierra Leone. The 2014–2015 Ebola outbreak was catastroph-ic in these countries, and its indirect impact of increasing the mortality rates of other diseases was also substantial.

Malaria morbidity and mortality in Ebola-affected countries caused by decreased health-care capacity, and the potential effect of mitigation strategies: a modelling analysis

Patrick G T Walker, Michael T White, Jamie T Griffin, Alison Reynolds, Neil M Ferguson, Azra C Ghani

Summary

Background: The ongoing Ebola epidemic in parts of west Africa largely overwhelmed health-care systems in 2014, making adequate care for malaria impossible and threatening the gains in malaria control achieved over the past
Where are we at in 2019?

post-Ebola syndrome

(Compare these numbers to total Ebola deaths)
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Urgent threats to control (and elimination)

• Resistance in mosquitoes
  – Pyrethroid resistance now widespread in some areas
  – DDT resistance

• Resistance in *Plasmodium*
  – ARTESUNATE RESISTANCE

• Complacency in the face of recent gains
  – Failing to “seal the deal” in the face of decreased prevalence
    • Diagnostics for submicroscopic disease
    • Establishing clinical impact of “subclinical” disease
Targeting Asymptomatic Malaria Infections: Active Surveillance in Control and Elimination

Hugh J. W. Sturrock1, Michelle S. Hsiang1,2, Justin M. Cohen3, David L. Smith4, Bryan Greenhouse5, Teun Bousema6,7, Roly D. Gosling1

Summary Points

- Active case detection (ACD) is a recommended intervention in low malaria transmission settings, yet evidence for its effectiveness is sparse.
- The potential of ACD to impact transmission is hampered by the ability of current field diagnostics to detect very low density infections and continued importation of parasites, as well as the operational challenges of achieving high coverage.
- The type of ACD employed should be guided by transmission setting and an understanding of risk factors.
- Standardized monitoring and evaluation of ACD strategies should be an integral component of ACD campaigns.
- In light of the current sensitivity of field diagnostic tests, targeted mass drug administration should be evaluated as an alternative or addition to ACD in low transmission settings.

Figure 1. Microepidemiology of malaria in villages of varying transmission setting. In moderate/high transmission settings (A), hotspots coalesce to form a more homogeneous pattern. In lower transmission settings (B), risk becomes increasingly spatially discrete, with single households or small groups of households experiencing higher exposure. In very low transmission settings (C), risk shifts to individual households or, where transmission is occurring outside the house/village, to individuals.

doi:10.1371/journal.pmed.1001467.g001
Additional cases detected with ultrasensitive RDT (10X ↑ sensitive)

**Summary Points**

- Active case detection (ACD) is a recommended intervention in low malaria transmission settings, yet evidence for its effectiveness is sparse.
- The potential of ACD to impact transmission is hampered by the ability of current field diagnostics to detect very low density infections and continued importation of parasites, as well as the operational challenges of achieving high coverage.
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- Standardized monitoring and evaluation of ACD strategies should be an integral component of ACD campaigns.
- In light of the current sensitivity of field diagnostic tests, targeted mass drug administration should be evaluated as an alternative or addition to ACD in low transmission settings.
The threat of artemisinin-resistant malaria

Figure 3 | The study site in Pailin, western Cambodia. Decreased artemisinin sensitivity was first detected in Pailin, western Cambodia, near the border with Thailand.


Urgent threats to control (and elimination) artesunate resistance

- Initially thought to be contained to small pockets SE Asia
- Now documented to be widespread in SE Asia
- New foci found in Guyana
- Looming threat in Africa
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Endgame thoughts

• Malaria is one of oldest foes
• Great advances made in last 15 years
• Can be eliminated in theory
• Major threats are present, however.
• **Endgame will require specific intensified concerted action despite decreasing cases**
  – Much more $$ per case averted
  – Politically difficult to maintain
  – Morbidity of other species, submicroscopic disease
Thank you