Rationale and Immunological Targets for Malaria Vaccines

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Malaria Disease Burden

WHO World malaria report 2011: (estimates based on 2010 data)

Population at risk: Over 3 billion

Mortality: estimated 655,000 deaths and 216 million cases in 2010.
>90% of deaths in Africa. >85% in children under 5 years old.

Over 50% reduction in cases in over 40 countries from 2000-2009
# Example of malaria control: Bioko Island

## Table 4

Mortality by any cause in children under 5 years of age recorded in surveys conducted on Bioko in 2004 and 2008, respectively, and recorded annual rainfall, March 1999 to February 2008

<table>
<thead>
<tr>
<th>Time period</th>
<th>Under-5 deaths</th>
<th>Follow-up, child-months</th>
<th>Under-5 mortality risk, deaths per 1000 births*</th>
<th>95% CI</th>
<th>Total rainfall† (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>March 2006–Feb. 2007</td>
<td>10</td>
<td>13,557</td>
<td>39</td>
<td>21–72</td>
<td>1696</td>
</tr>
<tr>
<td>March 2004–Feb. 2008</td>
<td>61</td>
<td>54,644</td>
<td>55</td>
<td>38–77</td>
<td>Mean 1710</td>
</tr>
</tbody>
</table>

* Estimated using Kaplan-Meier survival function.
† Malabo airport weather station.
Scaling-Up Malaria Control

**Preventive:** Long Lasting Insecticidal Nets and Indoor Residual Spraying in some settings

**Diagnosis:** Implementation of point-of-care rapid diagnostic testing

**Treatment:** Fully effective artemisinin-combination treatments.
Need for a vaccine…

- Malaria is an ongoing public health crisis (1 child every minute)

- Available measures have saved about 1 million lives in the last decade, and are highly cost-effective, but are not enough, and under threat by development of resistance

- A vaccine has been a long-hoped for addition to the armory

- What evidence is there that a vaccine is feasible?
A Malaria Vaccine is Feasible

Naturally acquired immunity
- Immunity to severe disease
  acquired rapidly – blood stage

Irradiated Sporozoite Immunity
- Model for liver stage immunity

Passive transfer of Immune IgG
- Directed at blood stage

Paediatric field proof of concept achieved
- GSK RTS,S/AS01
Naturally acquired Immunity: slow to develop, incomplete, and of limited duration

Vaccine must do better

*Parasite Immunology*, 2006, **28**, 51–60 Marsh & Kinyanjui
1 Hour: IgG

6 Days: CD8

7 Days: IgG

Passive: IgG
Life-cycle by parasite biomass

Aim: disease prevention

10^{(1)} sporozoites

10^{(11)} blood-stages

10^{(5)} gametocytes

10^{(5)} liver-stages
Life-cycle by parasite biomass

- liver-stages
  - $10^{(5)}$
- blood-stages
  - $10^{(11)}$
- gametocytes
  - $10^{(5)}$

Aim: prevention of transmission
<table>
<thead>
<tr>
<th>Target stage</th>
<th>Clinical effect</th>
<th>Antigens</th>
<th>Possible Immune mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevent infection</td>
<td>Pf, Pv CSP, TRAP, LSA1, LSA3</td>
<td>Humoral</td>
</tr>
<tr>
<td></td>
<td>Reduce clinical disease severity</td>
<td>MSP1, MSP2, AMA1, MSP3, GLURP, SERA, SR11.1, P27</td>
<td>Cell-Mediated</td>
</tr>
<tr>
<td></td>
<td>Interrupt transmission</td>
<td>PvS25, Pfs25, AgAPN1, Pfs230, Pfs48/45</td>
<td>Humoral</td>
</tr>
</tbody>
</table>
Global Malaria Vaccine Portfolio by Platform

Some unknowns from studies of immunity and biology

- What is the molecular basis of concomitant immunity & asymptomatic infection
- Can we induce more than strain-specific immunity?
- A lesson learned: adenovirus containing heterologous prime-boost regimens have induced the strongest CD8 responses in humans to date in malaria
Efficacy trials of malaria vaccines: Hierarchy of endpoints

Early field trials
n=300-1000

Challenge Trials
n=20-100

Challenge

Blood stage infection

Late field trials
n=2000-20000

Clinical malaria

Severe malaria

Death
Immunological basis of efficacy?

- No simple predictive correlate emerges from clinical trial data
- Very high titre IgG to conserved sporozoite surface antigenic component is associated with protection against infection
- CD4+ T cell responses are independently associated with protection in addition to IgG for RTS,S
Clinical Trial Arms Race: Costs are Rising

Augustine’s, not Moore’s law

<table>
<thead>
<tr>
<th>Year</th>
<th>Wright Model A</th>
<th>P-40 Kittyhawk</th>
<th>P-51 Mustang</th>
<th>F-16 Falcon</th>
<th>F-18 Hornet</th>
<th>F-35 JSF</th>
<th>F-15 Eagle</th>
<th>F-22 Raptor</th>
<th>F-14 Tomcat</th>
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<tbody>
<tr>
<td>1910</td>
<td>10^3</td>
<td>10^4</td>
<td>10^5</td>
<td>10^6</td>
<td>10^7</td>
<td>10^8</td>
<td>10^9</td>
<td>10^10</td>
<td>10^11</td>
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<tr>
<td>2020</td>
<td></td>
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</tbody>
</table>

Sources: Norman R. Augustine; John D. Christie

*Forecast

What the unit costs

Index of US military assets (number) and defence spending ($), 1970=100

Sources: IISS; US Government Printing Office
Working together to accelerate timelines

Information-sharing
Applying common-sense strategies to speed progress
Thank you!

For further info see WHO IVR website
- www.who.int/vaccine_research
- www.who.int/vaccine_research/Malaria/en/index.html
- Lancet Infectious Diseases March 2010 "Reducing Empiricism in Malaria Vaccine Design", Moorthy VS, Kieny MP