The RTS,S vaccine trials: further evidence for NSE or other explanations?

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Global malaria burden today

150 – 300 mio malaria cases/year, resulting in 300,000 – 600,000 deaths/year

(WHO 2015)
Impact of malaria control tools

Bhatt et al.
Nature 2015
Threats by drug & insecticide resistance development

**Artemisinin resistance**
Ashley et al. NEJM 2014

**Pyrethroid resistance**
Hemmingway et al. Lancet 2016
Need for malaria vaccines

Vaccine types:
1 = Pre-erythrocytic vaccines  
2 = Blood stage vaccines  
3 = Transmission blocking vaccines

Subunit vaccines (e.g. RTS,S)

Whole attenuated parasite approaches  
(e.g. sporozoites from γ-irradiated mosquitoes; immunization-treatment-vaccination, genetically attenuated sporozoites)
Challenges for malaria vaccines

- There is **no vaccine against a human parasite** until today.
- Although **natural immunity** to malaria develops in endemic areas, this generally **takes some years** of exposure and is **imperfect**.
- Extensive **immuno-epidemiological studies** have provided limited insight into what the best antigens for a vaccine might be.
- No good **animal models** for human malaria parasites.

**Nick White, Manson Tropical Diseases:** „Despite considerable effort and expense, a generally available and highly effective malaria vaccine is still unlikely in the future.“
It results from a collaboration, commenced in the 1980s, between the US Walter Reed Army Institute and GSK. A hybrid protein, formulated in an adjuvant named AS01. Initial vaccine constructs of CSP showed very low-level efficacy, but expressing the central repeat (‘R’) fused to the C-terminal region known to contain T cell epitopes (hence ‘T’) fused in turn to the hepatitis B surface antigen (‘S’) yielded a yeast-expressed protein RTS. To generate immunogenic particles, the RTS protein needed to be co-expressed with the ‘S’ protein to yield RTS,S.
History of RTS,S development

1984
- GSK/WRAIR initiate collaboration
- RTS,S first created by combining the malaria CS protein and hepatitis B surface antigen

1987
- RTS,S first created by combining the malaria CS protein and hepatitis B surface antigen
- Key proof-of-concept study shows 6 out of 7 volunteers in challenge trial are fully protected

1995
- First clinical tests in humans begin in adults in US

1997
- Key proof-of-concept study in children in Mozambique

1998
- First trials in Africa begin in Gambia

2001
- GSK/MVI partnership initiated

2004
- Key Phase II efficacy results in African children and infants published in The Lancet and NEJM

2007
- Phase II results in African children and infants published in The Lancet and NEJM

2009
- Phase III study start

2011
- Phase III study
- First results in 5-17 month olds 12 months follow up published in NEJM

2012
- Phase III study
- Second set of results in 6-12 week olds 12 months follow up published in the NEJM

2013
- Phase III study
- Results over 18 months follow-up first presented at MIM PAN African Malaria Conference with publication in PLoS Medicine 2014

2014
- File submitted to the European Medicine Agency (EMA)

2015
- Phase III study
- Final results including 3-4 years of follow-up and 4th dose of RTS,S administered 18 months after the third dose published in The Lancet

Kaslow & Biernaux Vaccine 2015
RTS,S phase III trial

Eleven study centres in 7 SSA countries (enrolment 03/2009 – 01/2011; follow-up until 01/2014)

- 6537 infants (6-12 weeks)
- 8922 children (5-17 months)

- Primary endpoint was the occurrence of malaria (passive case detection) after dose 3
Infants (6-12 wks): RTS,S or comparator with EPI vaccines (3 arms)

Children (5-17 mo): RTS,S or comparator (3 arms)

- Arm 1: Three times RTS,S + booster dose at 20 months
- Arm 2: Three times RTS,S + comparator at 20 months
- Arm 3: Comparator vac. (infants – meningococcal, children - rabies)
Final RTS,S trial results
- efficacy -

- Vaccine efficacy (VE) was 31\% in infants, and 66\% in children (12 months after dose 3)

- With and without booster dose, VE was 26\% and 18\% in infants and 36\% and 28\% in children (38/48 months after dose 1)

- VE against severe malaria reached 32\% in boostered children.

- VE became negative after prolonged follow-up in children exposed to higher transmission levels (5-7 years after dose 1)

Final RTS,S trial results
- adverse events -

RTS,S-specific:

❖ Increased risk for febrile convulsions (infants and children)
  - roughly 2/1000 RTS,S doses, 0.5/1000 comparator doses -

❖ Increased risk for meningitis (only children)
  - 21 cases in the two RTS,S groups, 1 in the control group –

❖ Increased risk for mortality, females (infants and children)
  - 123 cases in the two RTS,S groups, 33 in the control groups –

RTS,S Clinical Trial Partnership. Lancet 2015
## Final RTS,S trial results - mortality -

<table>
<thead>
<tr>
<th></th>
<th>R3R</th>
<th>R3C</th>
<th>C3C</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infants</strong></td>
<td>51</td>
<td>55</td>
<td>42</td>
<td>1.26 (0.89-1.80)</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td>61</td>
<td>46</td>
<td>46</td>
<td>1.22 (0.87-174)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>112</td>
<td>106</td>
<td>88</td>
<td>1.24 (0.97-158)</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td>50</td>
<td>45</td>
<td>55</td>
<td>0.84 (0.61-1.17)</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td>62</td>
<td>61</td>
<td>33</td>
<td>1.91 (1.30-2.79)</td>
</tr>
</tbody>
</table>

*Klein et al. mBio 2016; 7 e00514, modified by Greenwood 2016*
Final RTS,S trial results - adverse events -

Associated with successful malaria control:

- Increased malaria incidence over time
- Increased incidence in cerebral malaria (only in children)
  - 54 cases in the two RTS,S groups, 16 in the control group –

“Rebound malaria“ = An increase in malaria incidence after malaria control has been achieved above that which would have occurred without the intervention.

RTS,S Clinical Trial Partnership. *Lancet* 2015
RTS,S – conclusions

- RTS,S provides only modest and short-lived protection.
- Increased AEs and increased mortality are unexplained issues; reasons are unclear (different NSE of RTS,S/comparators?!)!
- Malaria vaccines in young children may lead to rebound morbidity (and probably mortality) in older age groups.
- Because of these residual questions about programmatic feasibility, preventive effect, and safety, the WHO recommended that more evidence be generated in pilot implementation studies (only 4 dose regimen in children) in 3-5 SSA countries with moderate-to-high levels of malaria transmission.