Malaria and Helminth

Ayola Akim ADEGNIKA
CERMEL; Lambaréné, Gabon
aadegnikaa@cermel.org
OVERVIEW

• Objectives
• Background
• Hypothesis
• Literature review
• Malaria and Helminthiasis in Gabon
  – Epidemiology
  – Vaccinology
• Conclusion
OBJECTIVES

• Reported effect of helminths infection on malaria
  – Effect of helminths on epidemiology of malaria
  – Effet of helminth on malaria vaccine candidates
  – Effect of helminths on malaria sexual stage
Helminths cause Heavy morbidity

- Malnutrition
- Learning/memory
- Anemia
- Weight loss
- Skin symptoms
- Immunopathology
- Permanent disability

Examples:
- Blood flukes (Schistosomes, filaria)
- Geohelminths (hookworm, Trichuris, Ascaris)
Helminth infections and Immunology

Response to helminth infection

- DC
- Th2 cell
- IL-4, IL-13
- B cell
- IgE
- Mast cell FceRI

Helminth

- Regulatory mechanisms
  - AAM
    - RELM-α
    - Ym 1/2
    - IL-10
    - TGF-β
  - Treg
    - IL-10
    - TGF-β
  - B cell
    - IL-10
  - Inhibitory antibodies

- Eosinophil
- IL-5
- IgE

- Worm killing
- Worm survival

Co-infection EDR

Danilowicz-Luebert et al., 2011
Helminths induce immune hypo responsiveness

Antigen specific T cell responses

Worm burden or time after infection

Chronic infection

Spill over suppression

IL-10, TGFβ
Malaria cause heavy mortality

• 207 million cases of malaria in 2012
• 627000 deaths caused by malaria in 2012
• 90% of cases occur in Africa
• Control is limited to:
  – ITNs
  – Indoor spray
  – Prompt case management treatment
  – No vaccine ➔ several underdevelopment
    • RTS ‘S in 2015???
Evidence in both humans and mice suggests:

- Early stage: type Th1 (IFN-γ)
- Later stage: type Treg
  - IgG1 et IgG3
Geographical distribution of malaria and helminthiasis

Malaria

Helminth

Geographic distribution of Malaria infection

Global distribution of soil-transmitted helminth infections

Areas where STH are a public health problem
Areas where STH are transmitted
Malaria and helminths co-infection

• How helminths infections affects malaria
  – Epidemiology?
  – Clinical features?
  – Vaccine candidates?
Malaria and helminths co-infection

• Several associations reported with different helminths species:
  – *Hookworm*
  – *A. lumbricoides*
  – *T. trichiura*
  – *M. Perstans*
  – *S. mansoni*
  – *S. hematobium*
Good worms, bad worms?

• **Good worms**
  – There is a trend towards a protective effect of *A. lumbricoides* and *S. hematobium* on incidence and pathogenesis of malaria.

• **Bad worms**
  – Hookworm and *S. mansoni* are positively associated with malaria incidence and pathogenesis.

• In general helminths protect against severe manifestations of malaria.
Good worms, bad worms?

- The observed Immunological trends:
  - Hookworms
  - *Trichuris trichiura*
  - *S. haematobium*
  - Associated with decreased level of antibody responses to *P. falciparum*
<table>
<thead>
<tr>
<th>Authors</th>
<th>Years</th>
<th>Co-infected</th>
<th>Malaria only</th>
<th>Standardized Mean Difference [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>INF-g</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilson</td>
<td>2009</td>
<td>10.85</td>
<td>11.02</td>
<td>-0.02 [-1.62, 1.6]</td>
</tr>
<tr>
<td>Nkone</td>
<td>2013</td>
<td>8.36</td>
<td>9.24</td>
<td>-0.82 [-1.6, 0.0]</td>
</tr>
<tr>
<td>Nkone</td>
<td>2013</td>
<td>5.3</td>
<td>5.34</td>
<td>0.0 [-0.8, 1.8]</td>
</tr>
<tr>
<td>Nmorsu</td>
<td>2009</td>
<td>6.22</td>
<td>6.02</td>
<td>-0.2 [-0.8, 0.4]</td>
</tr>
<tr>
<td>Metenou</td>
<td>2009</td>
<td>4.72</td>
<td>4.62</td>
<td>-0.1 [-0.8, 0.6]</td>
</tr>
<tr>
<td>Lyke</td>
<td>2006</td>
<td>3.52</td>
<td>3.42</td>
<td>0.1 [-0.8, 1.0]</td>
</tr>
<tr>
<td>Hartgers</td>
<td>2001</td>
<td>6.92</td>
<td>6.82</td>
<td>-0.1 [-0.8, 1.6]</td>
</tr>
<tr>
<td>Diallo</td>
<td>2010</td>
<td>3.54</td>
<td>3.44</td>
<td>0.1 [-0.8, 1.0]</td>
</tr>
<tr>
<td>Boef</td>
<td>2012</td>
<td>4.14</td>
<td>4.04</td>
<td>-0.1 [-0.8, 1.6]</td>
</tr>
<tr>
<td>RE Model for subgroup</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilson</td>
<td>2009</td>
<td>38.98</td>
<td>37.58</td>
<td>-0.3 [0.0, 0.6]</td>
</tr>
<tr>
<td>Nkone</td>
<td>2013</td>
<td>16.99</td>
<td>15.82</td>
<td>-0.1 [-0.8, 1.6]</td>
</tr>
<tr>
<td>Nmorsu</td>
<td>2009</td>
<td>8.06</td>
<td>8.06</td>
<td>0.0 [-0.8, 1.6]</td>
</tr>
<tr>
<td>Metenou</td>
<td>2009</td>
<td>8.92</td>
<td>8.92</td>
<td>0.0 [-0.8, 1.6]</td>
</tr>
<tr>
<td>Lyke</td>
<td>2006</td>
<td>8.92</td>
<td>8.92</td>
<td>0.0 [-0.8, 1.6]</td>
</tr>
<tr>
<td>Hartgers</td>
<td>2001</td>
<td>7.62</td>
<td>7.62</td>
<td>0.0 [-0.8, 1.6]</td>
</tr>
<tr>
<td>Diallo</td>
<td>2010</td>
<td>7.62</td>
<td>7.62</td>
<td>0.0 [-0.8, 1.6]</td>
</tr>
<tr>
<td>Boef</td>
<td>2012</td>
<td>7.62</td>
<td>7.62</td>
<td>0.0 [-0.8, 1.6]</td>
</tr>
<tr>
<td>RE Model for subgroup</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilson</td>
<td>2009</td>
<td>12.12</td>
<td>12.12</td>
<td>0.0 [-0.8, 1.6]</td>
</tr>
<tr>
<td>Nkone</td>
<td>2013</td>
<td>13.99</td>
<td>13.99</td>
<td>0.0 [-0.8, 1.6]</td>
</tr>
<tr>
<td>Nmorsu</td>
<td>2009</td>
<td>6.06</td>
<td>6.06</td>
<td>0.0 [-0.8, 1.6]</td>
</tr>
<tr>
<td>Metenou</td>
<td>2009</td>
<td>12.12</td>
<td>12.12</td>
<td>0.0 [-0.8, 1.6]</td>
</tr>
<tr>
<td>Lyke</td>
<td>2006</td>
<td>12.12</td>
<td>12.12</td>
<td>0.0 [-0.8, 1.6]</td>
</tr>
<tr>
<td>RE Model for subgroup</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nkone</td>
<td>2013</td>
<td>3.52</td>
<td>3.52</td>
<td>0.0 [-0.8, 1.6]</td>
</tr>
<tr>
<td>Lyke</td>
<td>2006</td>
<td>3.52</td>
<td>3.52</td>
<td>0.0 [-0.8, 1.6]</td>
</tr>
<tr>
<td>RE Model for subgroup</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nmorsu</td>
<td>2009</td>
<td>30.96</td>
<td>30.96</td>
<td>0.0 [-0.8, 1.6]</td>
</tr>
<tr>
<td>Lyke</td>
<td>2006</td>
<td>30.96</td>
<td>30.96</td>
<td>0.0 [-0.8, 1.6]</td>
</tr>
<tr>
<td>RE Model for subgroup</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-10d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilson</td>
<td>2009</td>
<td>79.54</td>
<td>79.54</td>
<td>0.0 [-0.8, 1.6]</td>
</tr>
<tr>
<td>Metenou</td>
<td>2009</td>
<td>79.54</td>
<td>79.54</td>
<td>0.0 [-0.8, 1.6]</td>
</tr>
<tr>
<td>Lyke</td>
<td>2006</td>
<td>17.85</td>
<td>17.85</td>
<td>0.0 [-0.8, 1.6]</td>
</tr>
<tr>
<td>RE model for all groups</td>
<td></td>
<td></td>
<td></td>
<td>0.02 [-0.46, 0.49]</td>
</tr>
</tbody>
</table>
Current malaria vaccine candidates are aiming to trigger a Th1 type immune response.
Helminths and vaccines

- TB
- TT
- INFLUENZA
- HIV
- Malaria
GMZ-2 trial développement

GMZ2 is a subunit vaccine of a fusion protein of MSP3 and GLURP in alum

Previous phase I clinical trials:

• European adults *(Esen et al. 2009)*
• African malaria-exposed adults *(Mordmuller et al 2011)*
• African malaria exposed children (1-5yrs) *(Belard et al. 2011)*
Antigen (GMZ2, GLURP & MSP3) specific antibodies are suppressed in *A. lumbricoides* and *T. trichiura* positive children (Esen et al 2012, In Press).
Total IgG: infected versus uninfected

Any helminth infection (A. lumbricoides & T. trichiura)

Impact of helminth infections on vaccination
Comments

• *T. trichiura* negatively affects IgG production
• *A. lumbricoides* seems to not affect IgG production
• Combined infection with both species has a stronger negative effect on IgG production
NEED FOR LARGE SAMPLE SIZE AND WELL DESIGNED STUDIES

IDEA STUDY

IDEA
Malaria vaccine candidate and helminths

General objective

To determine the modulation by worm co-infections on vaccination and vaccine-induced immune responses

Specific objectives

To assess the effect of worm co-infection on the efficacy of the malaria vaccine candidate (GMZ-2)

To assess the effect of worm co-infection on the humoral and cellular immune responses to GMZ-2
Method (1)

Design

Observational study nested into a phase IIb, randomized, controlled, double-blind, study to evaluate the efficacy, safety, and immunogenicity of GMZ2 malaria vaccine candidate.

Study population

Children aged from 1 to 5 years old living in Lambaréné and surrounding villages.

Vaccine allocation

1:1 randomization of either 3 doses of 100ug GMZ2 or HDC rabies vaccine at Day 0, 28 and 56.
Method (3)

Study flow chart

Urine and stool examination

Humoral response

Cell mediated immunity

Functionnal assay
Update on the work (1)

GMZ2 trials

512

IDEA worm and GMZ-2 study

411
Update on the work (3)

Preliminaries results/Microscopy

- Any helminth infection: 32%
  - Schistosomiasis: 9%
  - Intestinal helminth: 31%
    - T. trichura: 23%
    - A. lumbricoides: 12%
    - Hookworm: 2%
Samples collected and stored

Type and volume of samples collected at each timepoint

- PBMC
- anti-GMZ2-ELISA
- CBC
- Biochemistry
- Parasitemia

Visit number

dark blue $n = 411$, light blue $n = 100$; ELISA = serum/plasma
update

• Efficacy?????
• Immunogenicity????

➢ Final analysis => 2014 ????
Acknowledgments

Study participants

Investigators

THANK YOU FOR YOUR ATTENTION...