A Phase 1/2b double blind randomised controlled trial of the efficacy, safety and immunogenicity of heterologous prime-boost immunisation with the candidate malaria vaccines ChAd63 ME-TRAP and MVA ME-TRAP in 5-17 month old Burkinabe infants and children

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Malaria is the preeminent tropical infectious disease globally, with a devastating effect on human health and society.

The development of a vaccine against malaria is a high priority and of great importance in the context of coordinated efforts to reduce the burden of malaria.

ChAd63 ME-TRAP / MVA ME-TRAP heterologous prime-boost immunisation is a highly promising candidate malaria vaccination strategy. It shows durable partial efficacy in malaria challenge previous studies,
Primary Objective:

To assess the protective efficacy against clinical malaria of ChAd63 ME-TRAP / MVA ME-TRAP prime-boost immunisation, in 5-17 month old infants and children living in a malaria-endemic area, for 6 months after the last vaccination
Objectives

Secondary Objectives:

• **Duration of Protective efficacy against clinical malaria**
  
  To assess the protective efficacy against clinical malaria of ChAd63 ME-TRAP / MVA ME-TRAP prime-boost immunisation, in 5-17 month old infants and children living in a malaria-endemic area, for 12 and 24 months after the last vaccination.

• **Efficacy against asymptomatic *P. falciparum* infection**
  
  To assess the protective efficacy against asymptomatic *P. falciparum* infection of ChAd63 ME-TRAP / MVA ME-TRAP prime-boost immunisation, in 5-17 month old infants and children living in a malaria-endemic area, 6, 12 and 24 months after the last vaccination
Objectives

Secondary Objectives:

• **Efficacy against secondary case definitions of clinical malaria**

  To assess the protective efficacy against secondary case definitions of clinical malaria of ChAd63 ME-TRAP / MVA ME-TRAP prime-boost immunisation, in 5-17 month old infants and children living in a malaria-endemic area, for 6, 12 and 24 months after the last vaccination.

• **Safety objective**

  To assess the safety and reactogenicity of ChAd63 ME-TRAP / MVA ME-TRAP heterologous prime-boost immunisation, in 5-17 month old infants and children living in a malaria-endemic area, for 6, 12 and 24 months after the last vaccination.
Objectives

Secondary Objectives:

• **Immunogenicity objectives**

  - To assess the immunogenicity of ChAd63 ME-TRAP / MVA ME-TRAP heterologous prime-boost immunisation, in 5-17 month old infants and children living in a malaria-endemic area.

  - To explore the immunologic correlates of protective efficacy of ChAd63 ME-TRAP / MVA ME-TRAP prime-boost immunisation, in 5-17 month old infants and children living in a malaria-endemic area.
Objectives

*Exploratory Objective:*

- **Efficacy against incident cases of severe malaria**

  To assess the protective efficacy against severe malaria of ChAd63 ME-TRAP / MVA ME-TRAP prime-boost immunisation, in 5-17 month old infants and children living in a malaria-endemic area, for 6, 12 and 24 months after the last vaccination.
Study endpoints

- **Efficacy endpoints**
  
  - **Primary case definition of clinical malaria episode:**
    
    presence of - Axillary Temperature ≥37.5°C AND P. falciparum parasites density > 5000 asexuals forms/µL
  
  - **Secondary case definitions of clinical malaria episode**
    
    a) presence of - Axillary Temperature ≥37.5°C and/ or History of fever within the last 24 hours; AND - P. falciparum parasites density > 0

    b) presence of - Axillary Temperature ≥37.5°C; AND - P. falciparum parasites density > 500 asexuals forms/µL

    c) presence of - Axillary Temperature ≥37.5°C; AND - P. falciparum parasites density > 20,000 asexuals forms/µL

    **Either definition a) or b) or c) is sufficient for a secondary definition diagnosis of clinical malaria**
Study endpoints

• **Safety endpoints**
  
  • SAEs occurring from first vaccination until the end of the study

  • Local and systemic solicited and unsolicited adverse events, considered possibly, probably, or definitely related to vaccination, occurring from first vaccination until 1 month post second vaccination (study day 93).
Study endpoints

- **Immunogenicity endpoints**
  - T cell enumeration and characterisation, using ELISPOT, and flow cytometry with intracellular cytokine staining
  - Measurement of antibodies to TRAP and other malaria antigens, using ELISA
  - Measurement of antivector immune responses
  - Enumeration of antibody-secreting cells, using ELISPOT and flow cytometry
  - Cytokine quantification in serum, using ELISA
  - Evaluation of genetic determinants of immune responses and vaccine efficacy using HLA typing, DNA and RNA analysis of polymorphisms and transcript levels, detection of haemoglobin gene variants, and other suitable methods
  - Transcriptional profiling
Study site

- Banfora clinical trial site at about 400 km from Ouagadougou
- Covers a total population of 30,000 inhabitants.
- Bed net coverage ≈ 80%
- Malaria transmission occurs throughout the year, with a peak during the rainy season (June to October)
- Main malaria vectors are *Anopheles gambiae* and *Anopheles funestus*.
- Annual EIR varies from 55 to 400 infective bites/person/year.
Study site
Study site
Overview of the study Design

- Double-blinded, randomized controlled study, with an open-label lead-in safety evaluation
- 700 children enrolled in total
- Malaria vaccine candidate: ChAd63 ME-TRAP $5 \times 10^{10}$vp and MVA ME-TRAP $1 \times 10^{8}$ pfu
- Control vaccines: Verorab
- Three days active home visits post immunization to document solicited adverse events
- Unsolicited adverse events recorded from Day of first immunization till 1 month post 2nd vaccination
- SAEs recorded throughout the study duration
- Malaria cases documented by Passive Case surveillance methods
Schematic of study procedures

Blood sampling for exploratory immunology and/or Biological safety

Day 0 | Day 21 | Day 56 | Day 63 | Day 243

PASSIVE CASE SURVEILLANCE

AdCh63 ME-TRAP 5 x 10^{10} vp OR Rabies

MVA ME-TRAP 1 x 10^{8} pfu OR Rabies

Primary endpoint
Clinical malaria detection and Safety surveillance

- Health Facility of Siniena
- Health Facility of Tengrela
- Health Facility of Diaraba
- Health Facility of Bounouna
- Health Facility of Nafona
- Health Facility of Tarfila

Clinical research Unit of Banfora
Passive detection of uncomplicated malaria episodes

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Definition</th>
<th>Number of episodes recorded</th>
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<tbody>
<tr>
<td>Primary</td>
<td>$T\geq37.5^\circ C$ AND $P. f &gt; 5000$</td>
<td>800</td>
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<tr>
<td>Secondary 1</td>
<td>$T\geq37.5^\circ C$ and/ or History of fever AND $P. f &gt; 0$</td>
<td>1386</td>
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<tr>
<td>Secondary 2</td>
<td>$T\geq37.5^\circ C$ AND $P. f &gt; 500$</td>
<td>953</td>
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<tr>
<td>Secondary 3</td>
<td>$T\geq37.5^\circ C$ AND $P. f &gt; 20,000$</td>
<td>616</td>
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Current status & Next steps

- Follow up of the subjects completed
- Data entry and cleaning ongoing
- Study closeout visit scheduled in January 2015
- Full results disseminated Q2 2015
Conclusion

• Heterologous prime-boost vaccination with ChAd63 ME-TRAP prime, followed by MVA ME-TRAP boost, has shown durable partial efficacy against P. falciparum infection in a UK Adult Phase IIa sporozoite challenge study.

• The trial is the first Phase 2b study in children of this promising malaria vaccine candidate in endemic setting.

• Study vaccines appeared to be safe and well tolerated – Most of the solicited adverse events recorded were mild to moderate.

• These results will help define the potential role of these viral vectors, either used alone or as part of a multi-component vaccine, in malaria control in Africa.
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