PfSPZ Vaccine Administered by Direct Venous Inoculation to Prevent *Plasmodium falciparum* Malaria is as Safe as Normal Saline – a Meta-analysis of 13 Randomized Controlled Clinical Trials

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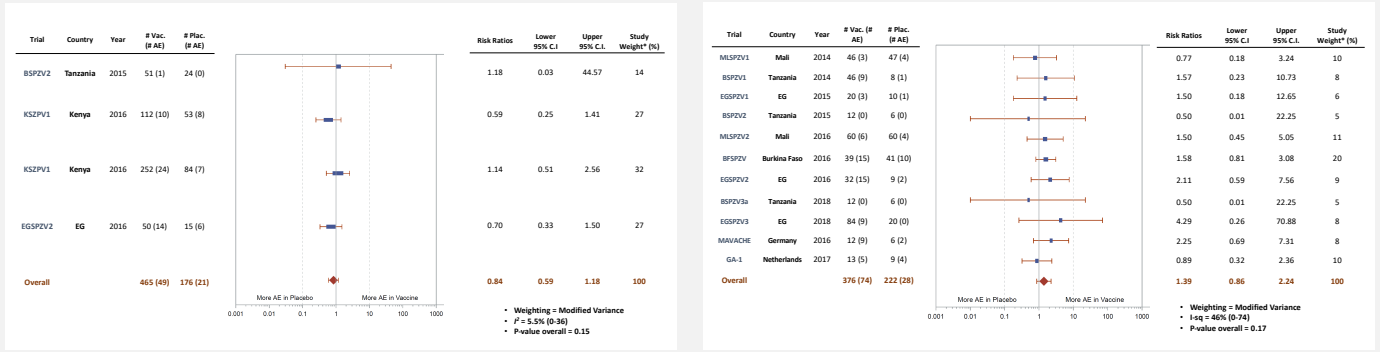
Introduction: The safety of Sanaria's PfSPZ Vaccine has been demonstrated in 17 active or completed phase 1 and 2 randomized, controlled trials (RCT) in adults in the US and EU and in infants, children and adults at multiple sites in sub-Saharan Africa. The vaccine is composed of radiation-attenuated, aseptic, purified, cryopreserved *Plasmodium falciparum* (Pf) sporozoites (SPZ) administered by direct venous inoculation (DVI) with Normal Saline (NS) as the comparator. Because the size of each RCT (18 to 336 subjects) limits the power of each trial we chose to further analyze the available safety data using meta-analysis.

Methods: Solicited adverse event (AE) data from all completed RCTs were included as either age ≥ 18 years (n=558) or age 5 months to 18 years (n=641). Any subject receiving at least one dose of PfSPZ Vaccine or NS was included. A random-effects model was used to study vaccine safety, and data evaluated using heterogeneity and I^2 statistic. Sensitivity analyses were conducted to assess the effects of dose, study population characteristics and zero-event trials. Chi-squared tests with continuity adjustment (Yates correction) were performed for each comparison between PfSPZ Vaccine and NS to prevent overestimation of statistical significance for the small data sets characterizing most of these trials.

Figure 1. Effect of vaccine on incidence of any solicited systemic adverse events per study subject – infants and children age 5 months to 18 years (left panel) and adults age ≥ 18 years (right panel).



Solicited systemic AE in adults and children age ≥ 6 years (≥ 9 years in KSPZV1) include fever (measured), subjective fever, headache, fatigue, malaise, myalgias, arthralgias and chills/rigors. Some studies included nausea/vomiting, diarrhea, abdominal pain, chest pain, palpitations, dyspnea or rash/pruritis/urticaria distant from the site of injection. Solicited systemic AE in children < age 6 years (< 9 years in KSPZV1) include fever (measured), subjective fever, rash/pruritis/urticaria, drowsiness, an inability or refusal to eat or drink or irritability/fussiness.

Conclusion:

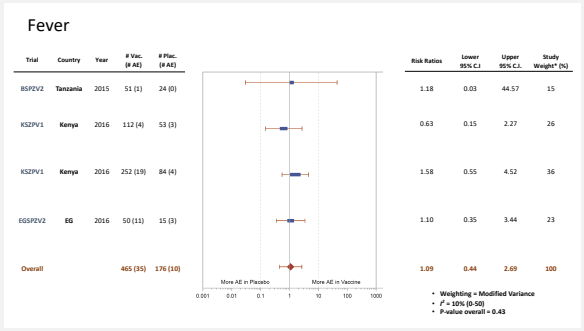
- In this meta-analysis of 13 randomized, double-blind, placebo-controlled trials no differences in the frequency of solicited adverse events between subjects receiving PfSPZ Vaccine or Normal Saline by DVI were identified.

Results: In children < 18 years there was no significant difference in the incidence of having any solicited systemic adverse event between PfSPZ Vaccine and NS (RR 0.84, CI 0.59-1.18) **(Figure 1)**. There was no significant difference in in the incidence of fever (RR 1.09, CI 0.44-2.69) or any solicited local adverse event between PfSPZ Vaccine and NS (RR 0.72, CI 0.29-1.82) **(Figure 2)**.

In adults age ≥ 18 years there was no significant difference in the incidence of having any solicited systemic adverse event between PfSPZ Vaccine and NS (RR 1.40, CI 0.83-2.38) **(Figure 1)**. This was also true for the incidence of headache (RR 1.22, CI 0.74-2.02) **(Figure 3)**, fever (RR 0.80, CI 0.58-1.10), fatigue (RR 0.74, CI 0.52-1.06), arthralgias (RR 0.74, CI 0.53-1.03), myalgias (RR 1.16, CI 0.87-1.55) **(Figure 3)** and any solicited local AE (RR 0.68, CI 0.10-4.84). Only 1 AE in 1 trial was of borderline significance in the chi-squared analysis (myalgias in BFPZV1, p=0.053). In all other comparisons p was > 0.2. In sensitivity analyses, no significant changes in risk ratio were observed when high vaccine dose trials (BFSPZV1, EGSPZV2), trials conducted in the EU (MAVACHE, GA-1) or trials with zero events of the AE under analysis were removed.

Figure 2. Effect of vaccine on incidence of fever and solicited local adverse events events per study subject - infants and children age 5 months - 18 years.

Fever



Any local AE

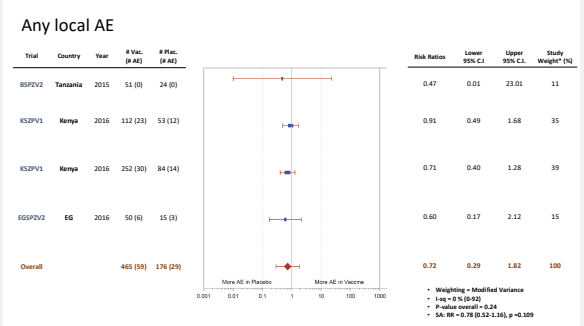
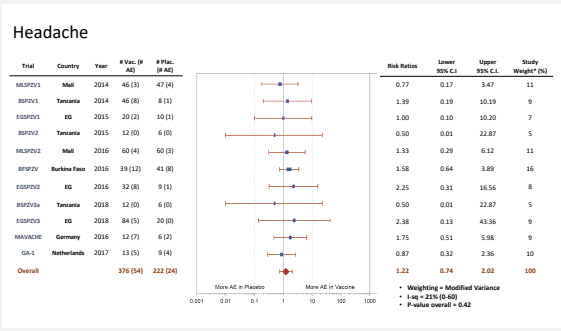
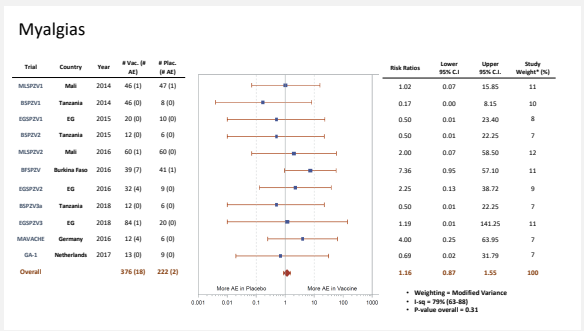


Figure 3. Effect of vaccine on incidence headache and myalgias per study subject - adults age ≥ 18 years.

Headache



Myalgias



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