Feasibility of Direct Venous Inoculation of the Radiation-Attenuated *Plasmodium falciparum* Whole Sporozoite Vaccine in Children and Infants in Siaya, Western Kenya

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PI, Paediatrician  
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Outline

- Trial design
- Rationale for giving vaccine via direct venous inoculation
- Shipment and storage
- Syringe preparation
- Injectors’ performance
- Pain perceptions
PfSPZ Vaccine Trial in Western Kenya

- **Part 1: Dose escalation/age de-escalation**
  - Children and infants 5 months–9 years of age
  - Focus on safety and tolerability
  - Blinded randomized controlled trial (RCT) administering 1 or 2 doses of PfSPZ Vaccine in escalating doses, with age de-escalation, follow-up for 28 days after vaccination

- **Part 2: Safety, efficacy and immunogenicity**
  - Infants 5–12 months of age
  - Blinded RCT administering 3 doses 8 weeks apart
  - Follow-up for 1 year following 3rd dose
Sanaria@ PfSPZ Vaccine

Aseptic, Purified, Vialized, Cryopreserved *Plasmodium falciparum* Sporozoites (PfSPZ) that Meet all Regulatory Standards

Radiation attenuated *Plasmodium falciparum* Sporozoites (PfSPZ)
Why ‘Direct Venous Inoculation’ (DVI)?

Results from previous studies

Protection against controlled human malaria infection (CHMI) in malaria-naïve volunteers (US)

- Intravenous/DVI versus intradermal or subcutaneous injection 3 weeks after 5 or 6 doses of $1.35 \times 10^5$ PfSPZ$^{1,2}$:
  - Intravenous route: 100% protection (6/6)
  - Intradermal or subcutaneous route: 0% protection (0/17)

- Intravenous versus intramuscular$^3$:
  - 4 doses of $2.2 \times 10^6$ PfSPZ Vaccine intramuscular:
    - 37.5% (3/8) of vaccinated subjects had short-term protection against CHMI and no protection at 6 months
  - 4 doses of $0.27 \times 10^6$ PfSPZ Vaccine intravenously:
    - 77.8% protection (7/9 volunteers) against CHMI at 3 weeks,
    - 75% (3/4 volunteers) protected at 23 weeks (overall 55%)

IV Administration of PfSPZ Vaccine Induces Systemic Priming of the Immune Response

Intramuscular or intradermal Injection:
- local antigen delivery: the antigens have to pass through the lymph nodes. Protection against malaria was low.

IV Injection:
- systemic antigen delivery to spleen, liver, and lymph nodes induces robust responses. Protection against malaria was high.
Cold Chain: Liquid Nitrogen Vapor Phase (LNVP) -180 C

No electricity required, Thermos-like container can hold vaccine stably for months
Vaccine Shipment and Storage

- **12 shipments**
  - 5–7 days from origin to site
  - 1 temp deviation due to customs delay

- **Storage**
  - No temperature deviation during storage
  - 4–8 kgs of LNVP added to the dry shipper weekly
Vaccine Preparation—Pharmacy Room

- PfSPZ Vaccine is thawed and diluted in human serum albumin and phosphate buffered saline
  - Appropriate dilutions made to achieve volume of 0.5ml (for all dose concentrations)
  - Time from thawing to injection not allowed to exceed 30 minutes
  - Activities in the pharmacy and injection room are controlled by timers
Estimated Syringe Preparation Times (for $1.8 \times 10^6$ PfSPZ Dose)
Vaccination Procedures—Injection Room

- Positioning and holding the hand/arm for injection is key for success
  - Time from syringe hand-off to injection shorter in older children than in infants
  - 2–3 staff needed for the injection process in toddlers and infants

<table>
<thead>
<tr>
<th>Time from Syringe Handoff from Pharmacy to Vaccine Injection (Minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 1</td>
</tr>
<tr>
<td>5–9 yrs</td>
</tr>
<tr>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Min, Max</td>
</tr>
</tbody>
</table>
Direct Venous Innoculation (DVI)

0.5 mL of diluted PfSPZ Vaccine is injected intravenously via insulin syringe and 25-gauge needle

- Alternative option – use of an intravenous cannula:
  - Pre-flush with 0.5 – 1 mL normal saline before injecting vaccine
  - Injection of vaccine/placebo
  - Post flush with 3 mL normal saline
DVI Assisted by Vein Viewer® (Christie Medical)
Vaccination Success, By Participant Age Group

Note: N represents participants.
*1 participant did not receive any study product at vaccination 1, but was vaccinated successfully at vaccination 2 and is not counted as failed venous access.
## Partial Injections By Age Group and Part 1 vs. 2, n/N (%)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Part 1</th>
<th>Part 2</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vacc 1</td>
<td>Vacc 2</td>
<td>Vacc 1</td>
</tr>
<tr>
<td>5-9 yrs</td>
<td>0/36 (0%)</td>
<td>1/23 (4.3%)</td>
<td>1/59 (1.7%)</td>
</tr>
<tr>
<td>13-59 mo</td>
<td>4/64 (6.3%)</td>
<td>1/22 (4.5%)</td>
<td>5/86 (5.8%)</td>
</tr>
<tr>
<td>5-12 mo</td>
<td>5/65 (7.7%)</td>
<td>0/23 (0%)</td>
<td>14/335 (4.2%)</td>
</tr>
</tbody>
</table>

Note: N represents vaccinations.
The majority (62%) of partial injections were estimated as 0.4 mL and above but below 0.5ml.
Number of Injection Attempts and Use of Cannula, By Age and Part 1 vs. 2*

Note: Ns refer to vaccinations
* In vaccinations where the complete 0.5 mL was administered.
** 4 of these 14 vaccinations involved 4 or more attempts.
Percent of Complete Vaccinations with 1 DVI in 5-12-Month-Olds, Over Time

P<0.001 for Fisher's Exact Test for trend over time.
The Injectors—Performance and Selection

- Injectors’ performance was observed during part 1, and the most successful injectors were selected for vaccinations in part 2.
- 10 injectors performed a varying number of vaccinations during part 1.
- 6 had a success rate over 80% and continued vaccinating during part 2.
- 2 of those 6 performed the majority of vaccinations in part 2.
### Participant Injection Sites in Part 2: Number with 1\textsuperscript{st} DVI Successful, by Site

<table>
<thead>
<tr>
<th>Arm (antecubital fossa)</th>
<th>Vacc 1</th>
<th>Vacc 2</th>
<th>Vacc 3</th>
<th>All vaccs</th>
<th>% of All Vaccs</th>
</tr>
</thead>
<tbody>
<tr>
<td>175</td>
<td>139</td>
<td>140</td>
<td>454</td>
<td>51</td>
<td></td>
</tr>
</tbody>
</table>

| Back of hand             | 113    | 165    | 147    | 425       | 47             |

| Right or left wrist      | 5      | 5      | 6      | 16        | 2              |

| Right or left foot       | 2      | 0      | 1      | 3         | <1             |
Vein Viewer Used in Part 2

- The vein viewer proved to be an excellent tool to identify poorly visible veins or to confirm the course of the palpated vein.

- It was used in:
  - 41% of all injection attempts for dose 1
  - 39% of all injection attempts for dose 2
  - 35% of all injection attempts for dose 3
Mothers’ Assessments of Pain Level

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Part</th>
<th>N</th>
<th>Pain Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>5-9 years</td>
<td>1</td>
<td>59</td>
<td>83%</td>
</tr>
<tr>
<td>13-59 months</td>
<td>1</td>
<td>86</td>
<td>53%</td>
</tr>
<tr>
<td>5-12 months</td>
<td>Parts 1 and 2</td>
<td>1,067</td>
<td>12%</td>
</tr>
</tbody>
</table>
### Vaccinations Where Children Cried Before, During, or After Injection, N (%)

<table>
<thead>
<tr>
<th></th>
<th>Part 1</th>
<th>Part 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5–9 years</td>
<td>13–59 months</td>
</tr>
<tr>
<td>N=59</td>
<td>N=87</td>
<td>N=88</td>
</tr>
<tr>
<td>8 (13.6)</td>
<td>61 (70.1)</td>
<td>74 (84.1)</td>
</tr>
</tbody>
</table>

- During 171/1067 (16%) vaccinations, infants did not cry during injection procedures.
- Some children continued breastfeeding,
- some slept throughout the injection.
Summary and Conclusions

- PfSPZ Vaccine storage, handling and preparation is possible in resource-limited settings
- Administration by DVI is feasible in infants and young children
  - These findings will also influence other vaccine trials where the intravenous route is more efficacious
- Injection teams showed progressively improving skills
- More than 90% of vaccinations could be given to infants with one single injection
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- KEMRI for all their support
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- Study staff
- Sanaria (sponsor) and all their staff for continuing support
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Thank you

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the KEMRI Center for Global Health Research.
Cannula used instead of DVI

- Part 1 – 13-59 months: 3/82 (3.7%)
- Part 1 – 5-12 months: 9/83 (10.8%)
- Part 2 – 5-12 months
  - Vaccination 1: 4/335 (1.2%)
  - Vaccination 2: 1/327 (0.3%)
  - Vaccination 3: 0
## Total number of injection attempts in those who received complete dose

<table>
<thead>
<tr>
<th>number of injections</th>
<th>5-9 years n/N(%)</th>
<th>13-59 months n/N(%)</th>
<th>5-12 months part 1 n/N(%)</th>
<th>5-12 months part 2 n/N(%)</th>
<th>All infants n/N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>154/59 (91.5)</td>
<td>71/82 (86.6)</td>
<td>70/83 (84.3)</td>
<td>897/963 (93.1)</td>
<td>967/1046 (92.4)</td>
</tr>
<tr>
<td>2</td>
<td>24/59 (6.8)</td>
<td>6/82 (7.2)</td>
<td>9/83 (10.8)</td>
<td>58/963 (6.0)</td>
<td>67/1046 (6.4)</td>
</tr>
<tr>
<td>3</td>
<td>31/59 (1.7)</td>
<td>5/82 (6.1)</td>
<td>4/83 (4.8)</td>
<td>5/963 (0.5)</td>
<td>9/1046 (0.9)</td>
</tr>
<tr>
<td>4 or more</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3/963 (0.3)</td>
<td>3/1046 (0.3)</td>
</tr>
<tr>
<td>Age Group</td>
<td>Part</td>
<td>N</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
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<td>------</td>
<td>------</td>
<td>----------</td>
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<td>1</td>
<td>59</td>
<td>83%</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>13-59 mos</td>
<td>1</td>
<td>86</td>
<td>53%</td>
<td>34%</td>
<td>8%</td>
</tr>
<tr>
<td>5-12 mos</td>
<td>1 [Vacc 1]</td>
<td>65</td>
<td>32%</td>
<td>42%</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>1 [Vacc 2]</td>
<td>23</td>
<td>17%</td>
<td>39%</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>88</td>
<td>28%</td>
<td>41%</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>2 [Vacc 1]</td>
<td>335</td>
<td>7%</td>
<td>31%</td>
<td>48%</td>
</tr>
<tr>
<td></td>
<td>2 [Vacc 2]</td>
<td>327</td>
<td>13%</td>
<td>39%</td>
<td>34%</td>
</tr>
<tr>
<td></td>
<td>2 [Vacc 3]</td>
<td>317</td>
<td>11%</td>
<td>37%</td>
<td>41%</td>
</tr>
<tr>
<td>2</td>
<td>979</td>
<td>11%</td>
<td>36%</td>
<td>41%</td>
<td>13%</td>
</tr>
<tr>
<td>All 5-12 months</td>
<td>Both 1 and 2</td>
<td>1067</td>
<td>12%</td>
<td>36%</td>
<td>40%</td>
</tr>
</tbody>
</table>
# Injectors performance

<table>
<thead>
<tr>
<th>Injector Number</th>
<th>Part 1 – number of vaccinations</th>
<th>Part 1 – successful at 1&lt;sup&gt;st&lt;/sup&gt; DVI (%)</th>
<th>Part 2 – number of vaccinations</th>
<th>Part 2 – % vaccinations successful at 1&lt;sup&gt;st&lt;/sup&gt; DVI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>92</td>
<td>410</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>96</td>
<td>540</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>91</td>
<td>45</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>89</td>
<td>11</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>22</td>
<td>86</td>
<td>15</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>92</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>67</td>
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<td></td>
</tr>
<tr>
<td>8</td>
<td>11</td>
<td>46</td>
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<td></td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>14</td>
<td>79</td>
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</table>
Storage and Delivery of the Vaccine in Liquid Nitrogen Vapor Phase (LNVP)

- LNVP use is widespread, especially in Africa
  - Veterinary medicine
    - 11 veterinary vaccines (East Coast Fever vaccine)
    - Artificial insemination of cattle (300-400 million cattle/year)
    - In Tanzania LNVP has revolutionized veterinary practice
  - All human *in vitro* fertilization and donor eggs and embryos
  - All human cellular therapies
  - All human cellular cancer vaccines
- LNVP for storage and delivery eliminates the need for electricity in cold chain
- Implementing a new vaccine in the EPI in Africa would cost the same for LNVP and standard cold chain
- For mass administration campaigns LNVP storage is preferable to 2-8°C
Distribution: Dry Shippers

Sanaria to Central Store


The ‘Last Mile’

http://www.alliance.rice.edu/images/alliance/Oneworld.JPG

http://www.wpro.who.int/NR/rdonlyres/4293A9CE-3C96-43CC-A859-8F8EBC2E5729/0/12_bg.jpg