IPTi and Serological Responses to EPI Vaccines

Prof. David Goldblatt, WHO Advisory Committee

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Background

- Concern that IPTi may interfere with responses to measles vaccine
- IPTi consortium funded by BMG Foundation to assist a co-ordinated research agenda for IPTi
- Possible to assess effect of IPTi on EPI responses in substudies nested within 5 RCT’s of the efficacy of IPTi in Africa
Aim

The aim of this analysis was to test the hypothesis that intermittent preventive treatment in infants (IPTi) with sulfadoxine-pyrimethamine (SP) does not have an adverse impact on serological responses to Expanded Programme on Immunization (EPI) vaccines.
Background

- Committee convened by WHO in 2003 to design and oversee the serological and statistical analysis of EPI responses and assess the influence of anti-malarials compared to placebo on EPI vaccine responses

- 3 face to face meetings, 12 teleconferences between 2003 and 2009
WHO Advisory Committee: 2003-2009

- **Professor Claire-Anne Siegrist (Chair)**, WHO Collaborating Centre for Neonatal Vaccinology, Centre Médical Universitaire, Geneva, Switzerland

- **Dr Paddy Farrington**, Dept Statistics, Open University, Milton Keynes, UK

- **Professor Peter Folb**, Chief Special Scientist, Medical Research Council, Cape Town, South Africa

- **Professor David Goldblatt**, Immunobiology Unit, Institute of Child Health, London, UK

- **Dr Omala Wimalaratne**, Dept Rabies and Vaccines, Medical Research Institute, Colombo, Sri Lanka

- **Dr Jane Crawley/Ms Tracey Goodman**, WHO Secretariat
Roles and Responsibilities

- WHO Advisory Committee (advice on study design and data interpretation; tendering and selection of laboratory)
  - Health Protection Agency, UK (all serological testing)
  - London School of Hygiene & Tropical Medicine (statistical analysis)
- 5 IPTi Efficacy Trials in Africa (samples)
- WHO EPI and GMP (coordination)
- Bill & Melinda Gates Foundation (funding)
## IPTi Trials and Antigens

<table>
<thead>
<tr>
<th>Study Site</th>
<th>IPTi Drugs*</th>
<th>Antigens Tested</th>
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</thead>
<tbody>
<tr>
<td><strong>Navrongo, Ghana</strong></td>
<td>SP**</td>
<td>Measles, Yellow Fever</td>
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<tr>
<td><strong>Manhiça, Mozambique</strong></td>
<td>SP</td>
<td>DTP, polio, Hep B, measles</td>
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<tr>
<td><strong>Bungoma, Kenya</strong></td>
<td>SP</td>
<td>DTP, polio, Hep B, Hib, measles</td>
</tr>
<tr>
<td><strong>Kisumu, Kenya</strong></td>
<td>SP/AQ/Art LapDap</td>
<td>DTP, polio, Hep B, Hib, measles</td>
</tr>
<tr>
<td><strong>Kilimanjaro, Tanzania</strong></td>
<td>SP, MQ LapDap</td>
<td>Measles</td>
</tr>
</tbody>
</table>

*Schedule: Three doses of IPTi given at DTP2, DTP3, and measles vaccination; **Navrongo gave 4th dose at 12 months.*
Endpoints

- Measles (primary endpoint)
  - Proportion of children receiving IPTi or placebo with protective titers (significant = >5%)
  - 500 infants per arm per site

- Other EPI antigens (secondary endpoints)
  - Proportion of children receiving IPTi or placebo with protective titers (significant = >10%)
  - 250 infants per arm per site

- Individual study and pooled analyses
Serological tests

- Blood samples
  - Post DTP3/HepB/Hib (at 18-20 weeks)
  - Pre & post measles & yellow fever (at 9 & 10-12 months)

- Post-vaccination geometric mean antibody titres/concentrations (GMT/GMC)
  - Plaque reduction neutralisation (measles, polio, YF)
  - Quantitative ELISA (other EPI antigens)
Advisory Committee Final Report

- Pooled analysis for SP/measles – Navrongo, Manhica, Kilimanjaro

- Pooled analysis for all drugs combined/measles – same as above plus Kisumu.

- Pooled Manhica & Kisumu for DTP, and Polio 1&3 (all drugs combined)

- Bungoma for other antigens/SP – individual analysis (not included in pooled)

- Bungoma & Kisumu for Hib – individual analysis

- Manhica, Bungoma, & Kisumu for HepB – individual analysis

- Navrongo for YF/SP – individual analysis
Results
Reverse Cumulative Distribution (RCD) Plot:

A graphic method for analysis of antibody data

Proportions above threshold
Results: Measles/SP
(Pooled Navrongo, Manhica, Kilimanjaro; n=1,646)
Results: Measles/All-drugs Combined*
(Pooled Navrongo, Manhica, Kisumu, Kilimanjaro; n=3,103)

* Except Kisumu LapDap
Results: DTP/All Drugs Combined
(Pooled Manhica and Kisumu)

Diphtheria (n=1,006)

Tetanus (n=700)

PertussisToxin (n=623)
### Results: Polio Types 1 & 3

(Pooled Manhica and Kisumu)

<table>
<thead>
<tr>
<th></th>
<th>Polio Type 1</th>
<th>Polio Type 3</th>
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<tbody>
<tr>
<td></td>
<td>(n=968)</td>
<td>(n=968)</td>
</tr>
<tr>
<td>Protective threshold</td>
<td>1 in 8 PRN</td>
<td>1 in 8 PRN</td>
</tr>
<tr>
<td>Percent unprotected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(below threshold)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>49/249</td>
<td>95/249</td>
</tr>
<tr>
<td></td>
<td>19.68%</td>
<td>38.15%</td>
</tr>
<tr>
<td>Combined</td>
<td>131/719</td>
<td>279/719</td>
</tr>
<tr>
<td></td>
<td>18.22%</td>
<td>38.80%</td>
</tr>
<tr>
<td>Difference Combined-Placebo</td>
<td>-1.46%</td>
<td>0.65%</td>
</tr>
<tr>
<td>Null hypothesis difference Combined-Placebo</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Test of non-inferiority</td>
<td>Z=-4.41, P&lt;0.0001⁺</td>
<td>Z=-2.70, P=0.004⁺</td>
</tr>
<tr>
<td>90%CI</td>
<td>(-6.23, 3.31)</td>
<td>(-5.23, 6.53)</td>
</tr>
<tr>
<td>95%CI</td>
<td>(-7.15, 4.23)</td>
<td>(-6.36, 7.66)</td>
</tr>
<tr>
<td>99%CI</td>
<td>(-8.93, 6.02)</td>
<td>(-8.56, 9.86)</td>
</tr>
</tbody>
</table>
Results: Hib
(Bungoma/SP & Kisumu/SP-ART, AQ-ART, LapDap)

Bungoma (n=425)  
Kisumu (n=997)
Results: HepB
(Manhica SP, Bungoma SP, and Kisumu other drugs)

Manhica n=494

Bungoma n=423
Yellow Fever Results
(Navrongo/SP n=136)

Reverse cumulative curve at yellow fever post vaccination
Conclusion of Advisory Committee

- Studies have demonstrated no adverse impact on the serological responses to DTP, polio, Hib, HepB and measles vaccines when the IPTi drugs SP, SP-ART, AQ-ART, and LapDap are given to infants at time of vaccination.

- IPTi-SP at the time of yellow fever vaccination, and IPTi-MQ with measles vaccination, have also shown to have no negative effect on the serological responses.