Vaccinations and child survival: The Optimunize study

I. Monitoring childhood interventions for child survival. DANIDA research training proposal
   1. Routine surveillance
   2. Determinants of delay
   3. Variation in implementation
   4. Out-of-sequence
   5. Sex-differences

II. Optimising the impact and cost-effectiveness of child health intervention programmes for vaccines and micronutrients in low-income countries. EU-funding
   1. Measure real life effects
   2. Combining observ. and RCT
   3. Multi-centre trial of early MV
   4. INDEPTH dissemination

III. Stimulate research in child interventions
   1. Help with analysis of data
   2. Workshops
   3. More trials
   4. Eradications research

INDEPTH Network
Associated: Rufiji, Vadu, Kisumu
Niakhar, Keneba

Chakaria
Nairobi
Kintampo

Navrongo
Nouna
Bandim

4 PhDs to submit thesis within next year

DANIDA-EU
4½ mill €
## Optimunise built on a paradigm conflict

<table>
<thead>
<tr>
<th>Mission</th>
<th>Single-disease-eradication paradigm</th>
<th>Non-specific immune training effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce mortality</td>
<td>Reduce mortality</td>
<td></td>
</tr>
<tr>
<td><strong>Focus</strong></td>
<td>Protective immune responses; clinical protection</td>
<td>Change in overall mortality – overall morbidity</td>
</tr>
<tr>
<td><strong>Effect</strong></td>
<td>Always beneficial, proportional to single-disease protection</td>
<td>Live vaccines -&gt; good effects – &gt; more than specific protection</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Same effect for boys and girls</td>
<td>Sex-differential effects are likely</td>
</tr>
<tr>
<td><strong>Sequence</strong></td>
<td>Give vaccines when possible</td>
<td>Live-vaccine-last should be policy</td>
</tr>
<tr>
<td><strong>Ultimate goal</strong></td>
<td>Eradicate – remove vaccine</td>
<td>Removing may have negative effect</td>
</tr>
</tbody>
</table>

*Live vaccines* -> good effects – > more than specific protection

*Inactivated vaccines* -> bad effect
SAGE Working Group on non-specific effects of vaccines (established March 2013)

Terms of Reference

WHO’s Strategic Advisory Group of Experts (SAGE) has requested the WHO Secretariat to review the evidence concerning the possible non-specific effects of vaccines included in the routine infant immunization schedule.

Preparatory to such a review of the evidence by SAGE in 2013, it is necessary to:

1. Systematically review all published and grey literature concerning epidemiological studies addressing “non-specific” effects of BCG, measles and DTP-containing vaccines on survival/all-cause mortality in children under five years of age and,

2. Critically appraise the evidence using the WHO Strategic Advisory Group of Experts (SAGE) guidelines.

The Working Group will be asked to determine if the current evidence is sufficient to lead to adjustments in policy recommendations or to warrant further scientific investigation, and if so, to define the path towards obtaining unequivocal evidence on these issues that would support future robust, evidence-based adjustments in immunization policies, if warranted.

Guidance for the development of evidence-based vaccine related recommendations.
WHO-SAGE estimates for different vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>ES (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>0.53 (0.40, 0.72)</td>
</tr>
<tr>
<td>DTP</td>
<td>1.38 (0.92, 2.08)</td>
</tr>
<tr>
<td>MCV</td>
<td>0.54 (0.45, 0.65)</td>
</tr>
</tbody>
</table>
Live vaccines have beneficial non-specific effects in randomised trials (RCTs)

Vaccines may train the immune system

<table>
<thead>
<tr>
<th>Randomised Trials</th>
<th>Outcome</th>
<th>Mortality rate ratio (MMR)</th>
<th>Censoring targeted deaths</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 RCTs of BCG at birth to LBW children</td>
<td>Neonatal mortality</td>
<td>0.59 (0.4-0.8)</td>
<td>0.59 (0.4-0.8)</td>
<td>JID 2011, PIDJ 2012</td>
</tr>
<tr>
<td>OPV0: BCG+OPV0 vs BCG</td>
<td>Infant mortality</td>
<td>0.68 (0.4-1.0)</td>
<td>0.68 (0.4-1.0)</td>
<td>CID 2015</td>
</tr>
<tr>
<td>RCT: MV at 4+9 vs 9 mo</td>
<td>Mortality 4-36 mo</td>
<td>0.70 (0.5-0.9)</td>
<td>0.74 (0.5-1.0)</td>
<td>BMJ 2010</td>
</tr>
</tbody>
</table>
### Campaigns

<table>
<thead>
<tr>
<th>Randomised Trials</th>
<th>15 OPV MRR after-OPV vs before-OPV</th>
<th>10 VAS MRR after-VAS vs before-VAS</th>
<th>1 H1N1 MRR after-H1N1 vs before-H1N1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A: 3 RCTs</td>
<td>0.75 (0.55-1.01)</td>
<td>1.47 (0.75-2.88)</td>
<td>6.48 (1.42-29.6)</td>
</tr>
<tr>
<td>Early MV</td>
<td>0.95 (0.71-1.28)</td>
<td>1.00 (0.70-1.43)</td>
<td></td>
</tr>
<tr>
<td>BCG at birth: 2 RCTs</td>
<td>0.81 (0.63-1.05)</td>
<td>0.68 (0.38-1.20)</td>
<td>2.16 (0.94-4.99)</td>
</tr>
<tr>
<td>OPV at birth</td>
<td>0.90 (0.61-1.32)</td>
<td>0.53 (0.16-1.68)</td>
<td>1.44 (0.52-3.96)</td>
</tr>
<tr>
<td>All</td>
<td>0.81 (0.70-0.95)</td>
<td>1.04 (0.80-1.35)</td>
<td>1.86 (1.02-3.42)</td>
</tr>
</tbody>
</table>
SAGE review 2014: The findings were inconsistent, with a majority of the studies indicating a detrimental effect of DTP, and two studies indicating a beneficial effect. Difficult to separate the effect of OPV and DTP.
### Introduction of DTP and OPV in Bissau 1981-1983

#### Before herd immunity

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Rate (deaths/pyrs)</th>
<th>Rate (deaths/pyrs)</th>
<th>HR DTP-only vs OPV-only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTP only</td>
<td>OPV-only</td>
<td></td>
</tr>
<tr>
<td>3-5</td>
<td>34.5 (6/17.4)</td>
<td>0 (0/8.6)</td>
<td>P=0.10</td>
</tr>
<tr>
<td>6-11</td>
<td>13.4 (9/67.1)</td>
<td>2.1 (1/48.4)</td>
<td>0.61 (0.8-52)</td>
</tr>
<tr>
<td>3-11</td>
<td>17.8 (15/84.5)</td>
<td>1.8 (1/57.0)</td>
<td>10.4 (1.4-79)</td>
</tr>
</tbody>
</table>
## RTS,S vaccine and child mortality

<table>
<thead>
<tr>
<th>Period</th>
<th>Deaths RTS,S vaccine</th>
<th>Deaths Controls</th>
<th>MRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14 mo</td>
<td>122/10306</td>
<td>56/5153</td>
<td>1.09 (0.80-1.49)</td>
</tr>
<tr>
<td>14 mo-end of study</td>
<td>96/10184</td>
<td>32/5097</td>
<td>1.50 (1.01-2.24)</td>
</tr>
<tr>
<td>Overall</td>
<td>218/10306</td>
<td>88/5153</td>
<td>1.24 (0.97-1.58)</td>
</tr>
</tbody>
</table>

Aaby et al  
Lancet 2015
Inactivated vaccines have negative effects for all-cause mortality for girls. Vaccines may misdirect the immune system.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Studies [Number]</th>
<th>Mortality rate ratio for vaccine vs unvaccinated</th>
<th>Mortality rate ratio for female vs male among vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTP</td>
<td>Obs. and natural experiments</td>
<td>2.00 (1.5-2.7) [8]</td>
<td>1.60 (1.4-1.9)[12]</td>
</tr>
<tr>
<td>IPV</td>
<td>3 RCTs</td>
<td>NA</td>
<td>1.52 (1.0-2.3)</td>
</tr>
<tr>
<td>HBV</td>
<td>1 natural experiment</td>
<td>1.81 (1.2-2.8)</td>
<td>2.20 (1.1-4.5)</td>
</tr>
<tr>
<td>Influ H1N1</td>
<td>1 natural experiment</td>
<td>1.86 (1.0-3.4)</td>
<td>Girls: 2.32 (1.2-4.5)</td>
</tr>
<tr>
<td>RTS,S malaria vaccine</td>
<td>2 RCTs</td>
<td>1.24 (1.0-1.6)</td>
<td>Long-T: 1.50(1.0-2.2)</td>
</tr>
</tbody>
</table>
Navrongo, Ghana 1990-2012: DTP >= MV from 86% to 1%

Stopping DTP >= MV

Explains 26% decline in mortality
GAVI: Vaccination status assessed at 12 months of age
Risk factors for not being fully immunized child (FIC) by 12 months: Lack of MV!

Not-FIC has 32% (18-47%) higher mortality from 1-3 yrs
Single-disease-eradication paradigm

Single disease perspective

Smallpox eradicated – vaccinia stopped
BCG stopped in high-income countries

Eradication planned within the next 10-20 years for Polio and Measles (and Rubella)

tOPV will be eradicated April 2016

No study examined the effect of stopping Vaccinia in 1980
But what if vaccinia had a beneficial effect?
Copenhagen school health cards had information on vaccinations => link to Danish health registers

Vaccinia removed in Bissau and Denmark in 1970s

Bissau 1998-2002 Vaccinia scar/no scar
40% (13-59%) reduction in mortality (Vaccine 2006)
1 scar: 35%; 2 scars: 46%; 3+ scars: 56% =>
Trend: 27% (5-44%) per scar

<table>
<thead>
<tr>
<th>Mortality 1971-2010</th>
<th>Natural causes of death (N=401)</th>
<th>Accident, suicides, murders (N=316)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths/pyrs</td>
<td>Adjusted HR</td>
</tr>
<tr>
<td>No vaccine</td>
<td>53/24414</td>
<td>1.0</td>
</tr>
<tr>
<td>Vaccinia + BCG</td>
<td>239/85618</td>
<td><strong>0.54 (0.36-0.81)</strong></td>
</tr>
<tr>
<td>Vaccinia or BCG</td>
<td>348/140036</td>
<td><strong>0.57 (0.40-0.81)</strong></td>
</tr>
</tbody>
</table>
The conflict between live and inactivated vaccines
Conflict between single disease and general training of the immune system
=> The domain of INDEPTH?

Under-5 mortality for girls in Bissau
The conflict between live and inactivated vaccines
Conflict between single disease and general training of the immune system
⇒ The domain of INDEPTH?
⇒ WG meets Thursday at 15:30-17:30

Under-5 mortality for girls in Bissau
Rural Bissau: MDG4 300/1000 to 97/1000 => 68%
This can only be understood with reference to vaccination campaigns
We started reading vaccinia and BCG scars in urban Bissau in 1998 and followed for mortality.

1893 individuals 25+ years in 1998 followed to 2002 (Vaccine 2006)

Vaccinia scar/no scar: Reduction in mortality 40% (13-59%)
1 scar: 35% ; 2 scars: 46% ; 3+ scars: 56% - trend: 27% (5-44%)/per scar
WHO’s Review of Measles vaccine

Measles vaccine reduced mortality by 46% (35-55%); effect stronger for girls
BCG reduced mortality by 47% (28-60%)
Implications: Campaigns not evaluated
17 years of campaigns in Guinea-Bissau

Polio and measles are not major killer diseases now so no effect on child survival expected. Effect of campaigns not measured
OPV reduced mortality rate by 19%; MV by 20%
Introduction of DTP and OPV in Bissau in 1981
Optimunise is built on a conflict of paradigms

Current paradigm: Single disease prevention

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<tr>
<th>Mission</th>
<th>Prevent specific disease to reduce mortality</th>
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<tbody>
<tr>
<td>Focus</td>
<td>Specific immune responses =&gt; Clinical protection =&gt; Reduction in mortality</td>
</tr>
<tr>
<td>Overall effect</td>
<td>Specific protection - always good</td>
</tr>
<tr>
<td>Sex</td>
<td>Same effect for boys and girls</td>
</tr>
<tr>
<td>Interaction</td>
<td>Age, maternal antibodies</td>
</tr>
<tr>
<td>Sequence</td>
<td>Give when possible; sequence does not matter</td>
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<td>Ultimate goal</td>
<td>Eradicate - save money by removing vaccine</td>
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GAVI collaboration – determinants of the fully immunized child (FIC) and the consequences of FIC for child survival

B. Mortality ratio of FIC vs non-FIC

<table>
<thead>
<tr>
<th>Routine registration by centre</th>
<th>Child mortality from 12-36 mos</th>
<th>Adjusted MRR for FIC versus – non-FIC</th>
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<tbody>
<tr>
<td>Navrongo</td>
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<td>Bandim</td>
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<td>Chakaria</td>
<td>0.84 (0.19-3.77)</td>
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<td>Nouna</td>
<td>0.75 (0.33-1.71)</td>
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<tr>
<td>All</td>
<td>0.78 (0.70-0.88)</td>
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This is MV versus Not MV => Measles vaccination coverage should be strengthened
GAVI collaboration – determinants of the fully immunized child (FIC) and the consequences of FIC for child survival

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This is MV versus Not MV =>
Measles vaccination coverage should be strengthened
3 RCTs of BCG-at-birth in LBW children

3-days MRR = 0.55 (0.32-0.93)
Neonatal MRR = 0.59 (0.44-0.81)

Neonatal MRR 0.28 (0.06-1.37) 0.55 (0.34-0.89) 0.66 (0.44-1.00)

Reduction in neonatal sepsis and respiratory infections

Not prevention of TB => Beneficial NSE of BCG
Navrongo: Neonatal mortality rates (day 1-28) and median age at BCG vaccination for home deliveries

- Median age BCG: 40 to 6 days
- Neonatal mortality: 3% to 1%
- No change for hospital deliveries
- INDEPTH should make neonatal mortality a priority
"The results indicated a beneficial effect of BCG on overall mortality. Estimated effects are in the region of a halving of mortality risk not likely to be attributable to any great extent to fewer deaths from tuberculosis."
Introduction of DTP
Rural areas of Guinea-Bissau 1984-87

Children aged 2-8 mo

Unvaccinated: travelling; sick; days without vaccines

DTP+ /no DTP 1.98 (1.03-3.79)
Female MRR 2.34 (1.04-5.27)

1-dose MRR 1.81 (1.0-3.5); 2-3 doses 4.36 (1.3-14.9)

Int J Epid 2004
Introduction of DTP

Urban areas of Guinea-Bissau 1981-88

Try to find more data but no other site may have data on introduction of DTP

Kaplan-Meier survival estimates

1-dose MRR 1.85 (1.00-3.5); 2-3-dose MRR 3.12 (1.44-6.8)
SAGE: “Most studies of DTP suggest detrimental effect – but inconsistent results”. Studies have survival bias!

- MRR unvac/Vaccinated <2.0
  - DTP had 94% Higher mortality

- MRR unvac/vaccinated >2.0
  - DTP has 61% lower mortality

Hazard Ratio of DTP vs no DTP

Hazard Ratio of unvaccinated vs vaccinated

MRR unvac/Vaccinated

GB-P
GB-D
GB-A
GB-E with surv bias
BF
India-E
India-A
Senegal
Ghana-A
Ghana-C
Malawi
India-G
PNG
RCTs of infant mortality for OPV0 vs no OPV0 – Censoring for OPV in campaigns
(No polio in Bissau)

<table>
<thead>
<tr>
<th>RCT-I#</th>
<th>Mortality rate ratio (MRR) for OPV0+BCG vs BCG-only</th>
</tr>
</thead>
<tbody>
<tr>
<td>All children</td>
<td>0.68 (0.43-1.00)</td>
</tr>
<tr>
<td>Boys</td>
<td>0.55 (0.33-0.95)</td>
</tr>
<tr>
<td>Girls</td>
<td>0.87 (0.48-1.56)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RCT-II###</th>
<th>MRR for OPV0 vs Vitamin A</th>
</tr>
</thead>
<tbody>
<tr>
<td>All LBW boys</td>
<td>0.68 (0.30-1.54)</td>
</tr>
</tbody>
</table>

# in review; #BMC Paediatrics 2014
25 OPV campaigns since 1998 to eradicate polio
Given to children aged 0-59 month

OPV reduced mortality by 22% => OPV campaigns interfere with results of RCTs

<table>
<thead>
<tr>
<th>Randomised Trials</th>
<th>Age-adjusted MRR after-OPV vs before-OPV</th>
<th>MRR without censoring for OPV campaigns</th>
<th>MRR with censoring for OPV campaigns</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 trials of neonatal Vit A</td>
<td>0.67 (0.53-0.85)</td>
<td>1.13 (0.94-1.34)</td>
<td>1.15 (0.80-1.65)</td>
</tr>
<tr>
<td>Early MV at 4½ +9 mo</td>
<td>0.72 (0.48-1.07)</td>
<td>0.70 (0.52-0.94)</td>
<td>0.42 (0.19-0.96)</td>
</tr>
<tr>
<td>BCG at birth I</td>
<td>0.91 (0.65-1.26)</td>
<td>0.83 (0.63-1.08)</td>
<td>0.78 (0.45-1.38)</td>
</tr>
<tr>
<td>OPV at birth</td>
<td>0.88 (0.60-1.30)</td>
<td>0.83 (0.61-1.13)</td>
<td>0.68 (0.45-1.00)</td>
</tr>
<tr>
<td>BCG at birthII</td>
<td>0.84 (0.62-1.13)</td>
<td>0.70 (0.47-1.04)</td>
<td>0.66 (0.44-1.00)</td>
</tr>
<tr>
<td>All</td>
<td>0.78 (0.68-0.90)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
H1N1 campaign has not been evaluated in low-income countries.

<table>
<thead>
<tr>
<th>Randomised Trial</th>
<th>Age-adjusted MRR after-H1N1 versus before-H1N1</th>
<th>Vitamin A group</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT of vitamin A versus placebo</td>
<td>1.68 (1.00-2.85)</td>
<td>2.83 (1.51-5.30)</td>
<td>0.76 (0.28-2.09)</td>
</tr>
</tbody>
</table>

This methodology could be used to evaluate campaigns at other INDEPTH centres.
Urban Bissau
MDG4 236/1000 to 68/1000 => 68%
Resolving the paradigm contradictions: The road to MDG4 is paved with OPV and measles vaccine (MV) campaigns.

MDG4 236/1000 to 68/1000 => 68%
Measles and polio to be eradicated – OPV and MV? Live vaccines have beneficial effects – when removed? Eradication paradigm: Smallpox vaccination in Guinea-B?

Study I  Scar/no scar: Reduction 40% (13-59%) (Vaccine 2006)
Study II Scar/no scar: Reduction 78% (39-92%) (PLoS ONE 2006)
Protection against HIV-1 for scar/no scar: Female 55% (9-78%) (Int J Epidemiol)
Denmark: Admissions for infections reduced by 16% (2-28%) (Int J Epidemiol)
BCG+vaccinia 43% (17-61%) reduction in mortality
Protection against HIV-1: Female 71% (7-91%) (not drug addicts)
INDEPTH and the NSEs of vaccines

New research opportunities and priorities for INDEPTH: SAGE/WHO has recommended further research into NSEs

• **IMMEDIATE ACTIONS BY WG** on VACCINES and interested centres
  1. Promote measles vaccination - ask GAVI for funding to improve coverage for MV; assure that MV and BCG are used to monitor the vaccination programme
  2. Study determinants of neonatal mortality and promote better BCG vaccination has strong beneficial effects on neonatal mortality
  3. Workshop on the impact of different campaigns (MV, OPV, Influenza, VAS)
  4. Workshop on the road to MDG4 in centres with long follow-up
  5. INDEPTH call for data on the introductions of routine vaccinations, in particular DTP (diphtheria-tetanus-pertussis) has strong negative effects on child survival

• **LONGTERM PLANS FOR INDEPTH**
  1. INDEPTH to promote data collection on routine interventions – e.g. included collection of such information in connection with verbal autopsies
  2. Confront the irrational DTP3 policy
  3. Confront the eradication paradigm – in relation to the eradication of polio and measles
  4. The vitamin A supplementation policy has failed – consider new strategies for Vitamin A supplementation
2014 an important year for the non-specific effects (NSE) of vaccines

**INDEPTH Vaccine network**
- EU Trials progressing to end Dec 2015
- GAVI contract
- PhD enrolment at Danish university

**New NSEs research opportunities and priorities**
- GAVI collaboration – measles vaccine (MV) is de-emphasised but MV associated with much better survival
- BCG has strong beneficial effects on neonatal mortality
- DTP (diphtheria-tetanus-pertussis) has strong negative effects on child survival
- The vitamin A supplementation policy has failed
- Oral polio vaccine (OPV) has major beneficial NSEs
- Campaigns with live vaccines have major impact on child survival
- Bandim has reached MDG4 in both urban and rural areas
- **SAGE/WHO has recommended further research into NSEs**
- INDEPTH should make NSE a major priority
WHO: No DTP problem or sex-differential effect (WER 2004)

However, the WHO-sponsored studies had survival bias:

1: Retrospective updating - dead children have no vaccine information
2: Children with no vaccine information assumed to be unvaccinated

=> Time after vaccination goes to vaccinated group; unknown deaths goes to unvaccinated group => too high mortality in “unvaccinated” group => Examine MRR for unvaccinated versus vaccinated children
Decade of national campaigns: 2000-2014

VAS = vitamin A supplementation
OPV = oral polio vaccine
MV = measles vaccine
H1N1 = influenza vaccine
The first RCT of VAS with Vaccines

Neonatal VAS also failed in Tanzania and Kintampo

Time for new studies Of VAS

**FIGURE 2**
Cumulative mortality according to gender and randomization to VAS/placebo. Note: Follow-up censored after 6 months of follow-up.
No polio in Bissau: OPV campaigns should have no effect on mortality

First OPV campaign in Bissau 1998: Mortality March-Dec

<table>
<thead>
<tr>
<th>OPV campaign in 1998 – age groups</th>
<th>1-2 doses of OPV</th>
<th>No OPV</th>
<th>Mortality rate ratio (MRR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 months</td>
<td>5%(28/553)</td>
<td>8%(19/238)</td>
<td>0.56 (0.3-1.0)</td>
</tr>
<tr>
<td>0-4 years</td>
<td>4%(143/3898)</td>
<td>6%(46/798)</td>
<td>0.67 (0.5-0.9)</td>
</tr>
</tbody>
</table>

Vaccine 2005

Campaigns have not been assessed for impact on survival
Bandim Health Project
A platform for testing real-life effects of health interventions since 1978

Guinea-Bissau

Bissau City

Urban study area
> 100,000 persons

Rural study area
> 100,000 persons in 180 villages

INDEPTH Working Group on Child survival – the impact of interventions in childhood
MV introduced mid-1970s based on antibody studies

Before-after measles vaccination:

Annual mortality rate in (INDEPTH) community studies

>50% reduction – how possible? Measles was 10-15% of deaths (WHO)

High-titre measles vaccine introduced 1989-withdrawn 1992 by WHO
HTMV was protective against measles

- A protective vaccine had negative non-specific effects
- Vaccines interact with sex – HTMV 2-fold higher mortality for girls
- 33% excess mortality 4 mo-5yrs – If not withdrawn ½ mill deaths/year in Africa

Effect due to DTP after MV
Vitamin A assumed to reduce mortality by 25% based on trials. However, recommended to be given with vaccines: Never tested!

Navrongo, Ghana, 1989-91; Mortality reduced by 19% (2-32%) (Lancet 93)

Not analysed by vaccination status

Mortality reduction in unvaccinated: 36% (12-53%); in vaccinated: 5% (-26-28%)

Random trial of VAS with vaccine in Bissau **no effect**
Global Health Interventions and the INDEPTH Network

Global Health has inherited a specific-disease-specific-intervention model with additive effects -

Contradictions identified by INDEPTH centres:
- **Live vaccines reduce mortality more than expected**
  - Measles vaccine reduce mortality by >40%
  - BCG reduce neonatal mortality by >40% in trials
- **Inactivated vaccines increased mortality for girls**
- **Effects are very often sex-differential**
- **Interventions very often interact:**
  - Vitamin A amplifies the non-specific effects of vaccines
  - Sequence or combination of vaccines is important

The immune system is a learning entity which can be enhanced or misdirected – if we controlled the system we had reached MDG4

WHO is currently reviewing the non-specific effects of vaccines (BCG, DTP, measles vaccine)
High-income: Infectious hospital admissions 
MMR vs. DTaP-IPV-Hib3 in Denmark

Hospital admission in 2nd year of life 
475,000 children in 1997-2006 – 44,000 hospital admission

DTP after MMR IRR=1.62 (1.28-2.05)

Sørup JAMA 2014;311:826-35
Introduction of DTP
Rural areas of Guinea-Bissau 1984-87

Children aged 2-8 mo

Unvaccinated: travelling; sick; days without vaccines

Survival probability

Follow-up (months)

DTP – (N=868)

DTP + (N=967)

DTP+ /no DTP 1.98 (1.03-3.79)

Female MRR 2.34 (1.04-5.27)

The only study in the global literature of effect on mortality of introduction of DTP

Int J Epid 2004
Differential effects of BCG, DTP and MV

### Table

<table>
<thead>
<tr>
<th>Location</th>
<th>BCG</th>
<th>DTP</th>
<th>MCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benin</td>
<td>0.68 (0.38-1.23)</td>
<td>2.20 (0.93-5.22)</td>
<td>0.36 (0.16-0.81)</td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>0.50 (0.34-0.75)</td>
<td>1.00 (0.60-1.67)</td>
<td>NA</td>
</tr>
<tr>
<td>Guinea-Bissau D</td>
<td>0.56 (0.37-0.84)</td>
<td>1.74 (1.10-2.75)</td>
<td>0.48 (0.27-0.87)</td>
</tr>
<tr>
<td>Guinea-Bissau A</td>
<td>0.55 (0.34-0.89)</td>
<td>4.33 (1.54-12.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Guinea-Bissau E</td>
<td>0.63 (0.30-1.33)</td>
<td>1.92 (1.04-3.52)</td>
<td>NA</td>
</tr>
<tr>
<td>India A</td>
<td>0.44 (0.29-0.66)</td>
<td>1.64 (0.87-3.07)</td>
<td>NA</td>
</tr>
<tr>
<td>Malawi</td>
<td>0.45 (0.16-1.23)</td>
<td>3.19 (0.80-12.8)</td>
<td>0.42 (0.16-1.14)</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>0.17 (0.09-0.34)</td>
<td>0.48 (0.22-1.09)</td>
<td>0.48 (0.18-1.26)</td>
</tr>
<tr>
<td>Senegal D</td>
<td>0.98 (0.50-1.90)</td>
<td>1.37 (0.54-3.47)</td>
<td>0.55 (0.31-0.98)</td>
</tr>
</tbody>
</table>
5 RCTs of early MV before 9 month had a cross-over design with the two groups getting a 2\textsuperscript{nd} vaccination after 9 months and followed to 3-5 years of age:

<table>
<thead>
<tr>
<th>Age</th>
<th>Early MV</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-5 months</td>
<td>Medium/ High titre MV</td>
<td>Inactivated Vaccine</td>
</tr>
<tr>
<td>9-10 months</td>
<td>Inactivated Vaccine</td>
<td>Standard MV</td>
</tr>
</tbody>
</table>

Mortality R. Ratio for inactivated vs MV 1.38 (1.05-1.80)
Bissau EZ1 Medium-titre EZ | 0.82 (0.30 to 2.20)
Bissau EZ2 Medium titre EZ | 1.95 (0.50 to 7.52)
Bissau EZ2 High-titre EZ | 1.88 (0.73 to 4.86)
Gambia High-titre EZ | 1/76.7 vs. 0/66.7
Senegal cohort 1-16 High-titre EZ and SW | 2.35 (1.13 to 4.88)
Senegal cohort 17-24 High-titre EZ | 1.75 (0.69 to 4.46)
Sudan High-titre EZ | 2.06 (0.62 to 6.82)

**5 RCTs inactivated versus MV = 89% (27-180%) higher mortality for girls**
Under-5 mortality in Bissau

MV

EPI/PAV

WAR

MV and OPV Campaigns Malaria?

DTP

DTP Booster

HBV

Deaths per 1000 live births

Year

Interactions: RCT of VAS with vaccines after 6 months
7585 children in urban and rural Bissau (2007-10)

Overall effect VAS vs placebo MRR = 0.93 (0.6-1.4)

P for same effect in boys and girls = 0.004
MDG4: Under-5 mortality for girls in Bissau

Post-war: Why decline?