WG Vaccinations and child survival: Where we are now!

I. Monitoring childhood interventions on 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. Eradication research

INDEPTH Network
Associated: Vadu
Interested: Ballabgarh, Rufiji, Kisumu, Niakhar, Farafenni, Dodowa
MDG4: Under-5 Mortality in Bissau (girls)

Deaths per 1000 live births

Year


MDG4 in 1 year Measles vaccine
Before-after measles vaccination (MV):
Annual mortality in community studies

How is this possible? Measles was not more than 10-15% of deaths
Not contradicted by any study!
Matlab - Randomised districts: 49% (28-58%) reduction
Navrongo - adjusted analysis: 49% (3-71%) reduction
Ballabgarh - before-after: 58% (16-79%) reduction
Vadu - crude estimate: 69% (20-88%) reduction
Measles vaccine versus no measles vaccine (IPV) at 6 months of age. War study. Bissau, 1998

5 RCTs at 4-9 mo in Sudan, Senegal, Gambia, Bissau: 0.20 (0.1-0.7) if DTP not given at the same time
Two MVs at 4 and 9 mo: 30% (6-49%) (F: 41% (9-62); M: 18%)
Measles censored 26% (0-46%)
(NB not against unvaccinated)

BMJ 2010

Significant reduction in admissions for lower respiratory infection
MDG4: Under-5 Mortality in Bissau (girls)
MDG4: Under-5 Mortality in Bissau (girls)

Deaths per 1000 live births

Year


EPI starts
Introduction of DTP
Rural areas of Guinea-Bissau 1984-87

Children aged 2-8 mo

Unvaccinated: travelling; sick; days without vaccines

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
1980: introduction of DTP and booster DTP; mortality rates by sex

**Guinea-Bissau 1992-94**

- Mortality rate (per 1000 years) vs. Age (months)
- Male and female mortality rates are shown with distinct lines.
- Bandwidth: 4 months

**Gambia 1998-2002**

- Mortality rate (per 1000 years) vs. Age (months)
- Male and female mortality rates are shown with distinct lines.
- Bandwidth: 4 months

**Navrongo, Ghana, 1994-99**

- Mortality rate (per 1000 years) vs. Age (months)
- Male and female mortality rates are shown with distinct lines.
- Ghana did not have booster DTP

**Senegal, Niakhar 1987-97**

- DTP1+BCG F/M MRR 0.57 (0.3-0.97)
- DTP3 F/M MRR 1.62 (0.9-3.1)

**Bissau and Gambia had booster DTP**
Early MV trials with cross-over

<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>

5 RCTs of early MV before 9 month in Sudan, Senegal, Gambia and Bissau had a cross-over design with the two groups getting a 2nd vaccination after 9 months and followed to 3-5 years of age:

Mortality Ratio for inactivated vs MV 1.38 (1.05-1.80)
<table>
<thead>
<tr>
<th>Location</th>
<th>Mortality Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bissau EZ1 Medium-titre EZ</td>
<td>0.82 (0.30 to 2.20)</td>
</tr>
<tr>
<td>Bissau EZ2 Medium titre EZ</td>
<td>1.95 (0.50 to 7.52)</td>
</tr>
<tr>
<td>Bissau EZ2 High-titre EZ</td>
<td>1.88 (0.73 to 4.86)</td>
</tr>
<tr>
<td>Gambia High-titre EZ</td>
<td>1/76.7 vs. 0/66.7</td>
</tr>
<tr>
<td>Senegal cohort 1-16 High-titre EZ and SW</td>
<td>2.35 (1.13 to 4.88)</td>
</tr>
<tr>
<td>Senegal cohort 17-24 High-titre EZ</td>
<td>1.75 (0.69 to 4.46)</td>
</tr>
<tr>
<td>Sudan High-titre EZ</td>
<td>2.06 (0.62 to 6.82)</td>
</tr>
</tbody>
</table>

5 RCTs inactivated versus MV = 89% (27-180%) higher mortality for girls
2 trials of BCG-at-birth in LBW children

Combined neonatal MRR=0.52 (0.33-0.82)
Within 3 days MRR=0.42 (0.19-0.92)

PIDJ 2012

JID 2011
Trends in neonatal mortality rates (excludes first day deaths) and median age at BCG vaccination for home deliveries in Navrongo HDSS: 2002-2011
Infectious hospital admissions in Denmark 1996-2006
MMR vs. DTaP-IPV-Hib3

DTaP-IPV-Hib3
IR=12.4
(22,120/178,763)

MMR1
IR=9.0
(22,772/254,296)

DTaP-IPV-Hib3
IR=12.6
(135/1074)

IRR=0.86 (0.84-0.88)

IRR=1.56 (1.25-1.95)

Also for morbidity. We are testing effect of BCG in RCT in Denmark
We justify our interventions in low-income countries by their impact on child survival:

“The GAVI Alliance was established in 2000 with a mission ..to saving children lives and protecting people’s health by increasing access to immunisation in poor countries”

But what we do in Global Health is preventing specific diseases! We measure

• specific disease burden; develop specific vaccines; specific immune responses; specific disease prevention and vaccine efficacy
• => Specific vaccine coverage and efficacy => equivalent to the planned reduction in morbidity and mortality
• That model was never documented in areas with high mortality - it was demonstrated to be wrong many times by INDEPTH centres
# INDEPTH centres and vaccine effects

<table>
<thead>
<tr>
<th>Vaccine effect</th>
<th>INDEPTH Centres</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles vaccine (MV) has beneficial effects not explained by prevention</td>
<td>Bandim, Niakhar, Bandafassi, Navrongo, Matlab, Vadu, Ballabgarh</td>
</tr>
<tr>
<td>High-titre MV – 2-fold higher mortality for girls =&gt; WHO withdrew high-titre MV</td>
<td>Bandim, Niakhar</td>
</tr>
<tr>
<td>MV has better effects for girls than for boys</td>
<td>Bandim, Niakhar, Bandafassi, Farrafenni, Navrongo</td>
</tr>
<tr>
<td>BCG has beneficial effects not explained by prevention of TB</td>
<td>Bandim, Navrongo, Vadu</td>
</tr>
<tr>
<td>OPV has beneficial effects</td>
<td>Bandim</td>
</tr>
<tr>
<td>Vaccinia had beneficial effects</td>
<td>Bandim</td>
</tr>
<tr>
<td>DTP has negative effects for girls</td>
<td>Bandim, Niakhar, Farrafenni, Navrongo, Vadu, Ballabgarh</td>
</tr>
<tr>
<td>DTP with MV or after MV worse than MV alone</td>
<td>Bandim, Niakhar, Navrongo, Vadu, Matlab</td>
</tr>
<tr>
<td>BCG+DTP1 reduces negative effects of DTP</td>
<td>Bandim, Niakhar, Vadu, Matlab</td>
</tr>
<tr>
<td>Vitamin A interacts with vaccines</td>
<td>Bandim, Navrongo</td>
</tr>
</tbody>
</table>
WHO’s Scientific Advisory Group of Experts (SAGE): Review of NSE of BCG, DTP and MV

<table>
<thead>
<tr>
<th>Background</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over the past two decades, a number of publications have claimed that several vaccines routinely administered to infants may have “non-specific” effects on mortality unrelated to prevention of illness and deaths caused by the specific diseases against which the vaccines have been formulated. For example, some authors have suggested that receipt of both BCG vaccine and measles vaccine is associated with a reduced risk of death (e.g. all cause mortality), while receipt of DTP vaccine is associated with an increased risk of death, at least among female infants. The vast majority of the evidence reporting these effects was generated using observational study designs (i.e. not randomized clinical trials) that are afflicted by the risk of bias, and as a result, poorly-controlled or uncontrolled confounding and various types of selection and information bias have been suggested as alternative explanations for these findings.</td>
</tr>
</tbody>
</table>

- Decision in 2014 about policy changes or additional studies
  ⇒ Many possibilities for INDEPTH
- **Best-case scenario:** Policy changes to be made – fields studies have to be conducted
- **Worst-case scenario:** NSE dismissed - methodological incorrect
- More **INDEPTH** studies needed to document the importance of NSE!
<table>
<thead>
<tr>
<th>Best-case scenarios: Policy change needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Earlier BCG to reduced neonatal mortality</td>
</tr>
<tr>
<td>2. Earlier MV to reduce child mortality in general</td>
</tr>
<tr>
<td>3. The effect of the 2nd dose of MV at 18 months</td>
</tr>
<tr>
<td>4. Not give DTP after MV</td>
</tr>
<tr>
<td>5. Trials to reduce the negative effect of DTP</td>
</tr>
<tr>
<td>6. Not use DTP3 as performance indicator for EPIs</td>
</tr>
<tr>
<td>7. Redefine the Vitamin A supplementation policy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Worst-case scenarios: NSE rejected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. WHO has no study to support their current policy so they can only reject for methodological reasons</td>
</tr>
<tr>
<td>2. Eradication research – smallpox</td>
</tr>
<tr>
<td>3. OPV will be replaced with IPV</td>
</tr>
<tr>
<td>4. What will happen when measles and polio eradicated? =&gt; Live vaccines will be reduced and DTP will be last</td>
</tr>
</tbody>
</table>
MDG4: Under-5 mortality in Bissau

1: MV
2: EPI DTP
3: Post-war

Year
Deaths per 1000 live births
Specific disease => Eradication!
Measles vaccine campaigns during the last 15 years: No study

Compared mortality after campaign with two years before

<table>
<thead>
<tr>
<th>MV campaign in May 2006 – age groups</th>
<th>Mortality June-May 2006-7</th>
<th>Mortality June-May 2004-6</th>
<th>Mortality rate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-11 months</td>
<td>5.1%(41/806)</td>
<td>6.1%(100/1649)</td>
<td>0.84(0.58-1.22)</td>
</tr>
<tr>
<td>1-4 years</td>
<td>2.1%(123/5973)</td>
<td>2.7%(315/11681)</td>
<td>0.76(0.62-0.94)</td>
</tr>
</tbody>
</table>

We have found in randomised trial that the 2\textsuperscript{nd} dose of MV was associated with a 29% reduction in mortality compared with the current policy of one dose => MV campaigns may lower overall mortality
The vaccine group has written a draft paper

INDEPTH RESEARCH PLATFORM FOR VACCINES AND OTHER CHILDHOOD INTERVENTIONS: REACHING MDG4 AND BEYOND

(send a mail to p.aaby@bandim.org to get it)

To be discussed on Wednesday 15:30-17:30
Global Health has inherited a specific-disease-specific-intervention model with additive effects - if measles is 10% and rotavirus 5% of deaths then MV + rotavirus vaccine = 15% reduction. All policy decisions are based on this model. This model has been contradicted numerous times.

Global Health has yet to learn from the contradictions found in all the INDEPTH sites:
- Live vaccines reduce mortality more than expected
- Inactivated vaccines have negative effects for female survival
- Early training of immunity have long-term effect
- Effects are very often sex-differential
- Interventions very often interact

The immune system is a learning entity which can be enhanced or misdirected – e.g. BCG reprograms monocytes to nonspecific protection. If we had controlled the system we had reached MDG4.
Polio campaigns during the last 15-20 years: No study

First OPV campaign in Bissau 1998 - Mortality March-Dec 1998

<table>
<thead>
<tr>
<th>OPV campaign in 1998 – age groups</th>
<th>Mortality for 1-2 doses of OPV</th>
<th>Mortality for No OPV</th>
<th>Mortality rate ratio (MRR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 months</td>
<td>5.1%(28/553)</td>
<td>8.0%(19/238)</td>
<td>0.56 (0.3-1.0)</td>
</tr>
<tr>
<td>0-4 years</td>
<td>3.7%(143/3898)</td>
<td>5.8%(46/798)</td>
<td>0.67 (0.5-0.9)</td>
</tr>
</tbody>
</table>

DTP was missing in Bissau in 2001. Some children got OPV only at the health centre whereas other had both OPV+DTP. Hospital fatality was 3-fold lower = 0.29 (0.11-0.77) for OPV only
Best-case and worst-cases scenario:

**Best-case scenarios: Policy change needed**
1. Earlier BCG to reduced neonatal mortality
2. Earlier MV to reduce child mortality in general
3. The effect of the 2nd dose of MV at 18 months
4. Increase coverage for MV
5. Not give DTP after MV
6. Trials to reduce the negative effect of DTP
7. Get rid of DTP3 as the main performance indicator for vaccine programs
8. Redefine the Vitamin A supplementation policy

**Worst-case scenarios: NSE rejected**
1. Confront the methodological issues
2. WHO has no study to support their current policy
3. Eradication research – smallpox
4. What will happen when measles and polio eradicated
5. OPV will be replaced with IPV
6. Live vaccine will be reduced and DTP will be last
Mortality after BCG+DTP1-first versus BCG or DTP1-first (2-8 mo - before MV)

<table>
<thead>
<tr>
<th>Study</th>
<th>Deaths/person-years [N]</th>
<th>MRR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BCG+DTP1</td>
<td>BCG or DTP1</td>
</tr>
<tr>
<td>Niakhar, Senegal, 1997-99</td>
<td>53 (90/1697)</td>
<td>70 (41/584)</td>
</tr>
<tr>
<td>Vadu, India, 1987-89</td>
<td>5 (1/187)</td>
<td>23 (19/811)</td>
</tr>
<tr>
<td>Matlab, Bangladesh, 1986-99</td>
<td>16 (164/10286)</td>
<td>32 (102/3234)</td>
</tr>
<tr>
<td>Bissau, LBW, 2004-2008</td>
<td>55 (4/73)</td>
<td>100 (20/201)</td>
</tr>
<tr>
<td>Meta</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This strategy reduces particularly female mortality
Introducing BCG in Norrbotten, Sweden, 1927-31: Mortality at 0-4 years - 20,000 children

This made little sense

Reduction was in infancy, but TB deaths occur later

“One could evidently be tempted to find an explanation for this much lower mortality among vaccinated children in the idea that BCG provokes a non-specific immunity...” Carl Naeslund 1932
Example 1: Measles vaccination
Testing non-specific effects (NSE) of MV

Recruitment 2003-2007 – 6,600 randomised; Follow-up to 2009
Study designed to test a 25% difference in mortality
MV at 4+9mo vs MV at 9mo by Vitamin A-at-birth status

Vitamin A Placebo

DTP3+MV 9 mo

P=0.012

Vitamin A may have a fundamental impact on the NSEs

Only those who did not receive VAS-at-birth

BMJ 2010
Risk assessment for early use of EZ measles vaccine: Role of maternal antibodies

Figure 1: Kaplan-Meier accumulated mortality curves between 4½ months and 5 years of age.
Effect of maternal antibodies (matab) in two-dose measles vaccine trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Deaths/person-years [N]</th>
<th>MRR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MV with matab</td>
<td>MV with no matab</td>
</tr>
<tr>
<td>1993-1995</td>
<td>0/121.0 [27]</td>
<td>16/494.9 [123]</td>
</tr>
<tr>
<td>2003-2007</td>
<td>3/908 [233]</td>
<td>11/760 [201]</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Example 2: BCG vs DTP
Mortality by vaccination status for children aged 0-6 mo at initial visit – 6 mo follow-up, rural areas

Survival probability

Follow-up (months)

BCG+ / BCG- 0.55 (0.36-0.85)
DTP+ / DTP- 1.84 (1.10-3.10)

BCG # DTP

BMJ 2000
RCT1: Testing NSE of BCG

BCG not given to LBW children => RCT justified
- We recruited LBW children at maternity ward – 11/2004-1/2008
- Randomising to BCG-at-birth or later (as normal)
- Driven home from hospital to be able to identify and follow later
- Visited at 2, 6, and 12 months
The VAS effect differed in children with (N=6,656) and without (N=5,066) a health card (P=0.06) - due to differential effect of VAS in girls (P<0.01)
Some recent results

Randomized trial testing the effect of vitamin A with vaccines to children > 6 months

Enrolling 7585 children in urban and rural Guinea-Bissau between 2007-2010

Overall effect: MRR=1.02 (0.69-1.51)

P for same effect in boys and girls=0.01

Ane Fisker, PhD thesis
WG: PhD – project: Routine registration of childhood interventions (DANIDA)

Phase I (2010-15): Improve routine data collection on vaccinations => to facilitate observational studies and decide on priority trials

Research training (PhD) proposal approved by Danida: Monitoring the impact of childhood interventions on child survival and morbidity (Ballabgarh, Navrongo, Nouna, Nairobi, Kintampo, Bandim)
WG-III: PhD – project: Routine registration of childhood interventions

Common data collection methodology:
- special teams for data collection or integrated in general census;
- children under 3 years of age,
- 3-4 yearly rounds,
- birth form,
- verbal autopsy: collection of vaccination cards
- SES and nutritional status
- document other interventions (vitamin A etc) and campaign
- Assure that unvaccinated group is properly defined – and why not vaccinated
- Registration of hospitalisations
- Date of data collection always documented
- Focus on possible sex-differential bias and effects
WG: PhD – project: Routine registration of childhood interventions

Monitoring the impact of childhood interventions on child survival and morbidity:

Phase I: Improved data collection methodology
Phase II: Determine risk factors for delay in vaccination and micronutrient delivery
Phase III: Analysis and writing papers for the PhD

Workshops – sites visits:
A. Data collection methodology – Bissau, Feb 2011
B. Statistical analyses/Stata – Accra, January 2012
C. Statistical analyses – Biissau, December/Jan 2013
D. Follow-up meetings at all AGMs 2009-2012
E. Sites visits to Navrongo, Nouna, Nairobi, Nouna, Kintampo – more will be planned
F. Training in Copenhagen: Paul Navrongo in 2010; Martin Nairobi 2012
WG: PhD – project: Site visits

Better use of vaccination data from health centres:
- likely to be better than 3-monthly surveys
- likely to be better than Verbal autopsy data

Use health centre and hospital data for morbidity outcome:
- likely to be better than 3-monthly surveys

Use variation in programme implementation for "natural experiments" – examples: Nouna, Navrongo

More focus on
- Campaigns – not collected previously
- Data quality
WG: PhD – project: Routine registration of childhood interventions

Major Problems:

Enrolment of PhD students at national universities – has been a nightmare: no one is interested, documents delayed, no response, no supervisors, MPhil requirements, etc

Ballabgard – has dropped out, not responded, PhD students only interested in non-Indian PhD

=> replace with Chakaria if possible

Students too many other things to do, junior position in their institution

The process of data collection, date entry, detecting errors, revisions – too slow
WG-II: Reanalysis of existing data

- Analyses of existing data: we can do a lot more with existing data
  - Farafenni => Routine vaccinations and child mortality (Vaccine 2007)
  - Navrongo => Vaccines and vitamin A (AJCN 2009)
  - Ballabgard => Significant Vaccination Delay can Occur Even in a Community with Very High Vaccination Coverage: Evidence from Ballabgarh, India (J Trop Pediatr, 2011)
  - Nairobi => Determinants of non-vaccination (BMC Public Health 2010)
  - Navrongo => Non-specific effects of vaccination (data from vitamin A trial) (TMIH, in revision)
  - Vadu => Analysis of out-of-sequence vaccination data from Vadu (Vaccine, in review)
  - Nouna => Vaccination coverage (draft paper)
  - Bandim => Change in vaccination schedule (draft)

- Started analysis of the first cross site paper: The impact of nutritional status on time to vaccination (Vadu, Bissau, Malawi)
- Re-analysis of the data from Bangladesh

- Several other people have said they have data for analysis (Kisumu, Rufiji, Ifakara, Dodowa)
## Median age of BCG at Indepth sites

<table>
<thead>
<tr>
<th>Sites</th>
<th>Median age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bandim (urban)</td>
<td>2 days</td>
</tr>
<tr>
<td>Nouna</td>
<td>14 days</td>
</tr>
<tr>
<td>Navrongo</td>
<td>4 days</td>
</tr>
<tr>
<td>Kintampo</td>
<td>22 days</td>
</tr>
<tr>
<td>Rural Bissau</td>
<td>40 days</td>
</tr>
</tbody>
</table>
WG: Multi-centre study on cost-effectiveness of interventions, including trial of early MV

EU proposal: ”Optimising the impact and cost-effectiveness of existing child health intervention programmes for vaccines and micronutrients in low-income countries” (Navrongo, Nouna, Bandim)

To support common data collection methodology and analysis of the impact of routine vaccinations and other interventions in childhood

Develop a methodology to assess ”real life” effects of health programmes and evaluate the cost effectiveness and suggest possible modifications => conduct new trials

Conduct a multicentre trial of early measles vaccination at 4 months
WG: Multi-centre study on cost-effectiveness of interventions, including trial of early MV

Consortium meetings: 4/2011 (Navrongo), 3/2012 (Nouna), Bandim 1/2013

Data collection methodology and statistical workshops – overlap Danida

Measles vaccination protocol to be submitted this month (April 2012)

Workshop to develop procedures for trial and manual for data collection (May 2012)

Problems:

We have been delayed – partly my fault

Decline in mortality and change in Vaccination schedule (MV at 18 mo in Ghana)
Testing NSE of MV at 3 INDEPTH sites

Hypothesis: 50% reduction per site; 32% in combined analysis
Decline in mortality and change in Vaccination schedule (MV at 18 mo in Ghana)
Smallpox gone

Measles and Polio within the next 10-15 years

Specific disease Focus vs general Resistance

The eradication of measles infection may increase child mortality in Africa

Trying BCG in Denmark against atopic disease
Bacille Calmette-Guérin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes

Johanneke Kleinnijenhuis\textsuperscript{a,b,1}, Jessica Quintin\textsuperscript{a,b,1}, Frank Preijers\textsuperscript{c}, Leo A. B. Joosten\textsuperscript{a,b}, Daniela C. Ifrim\textsuperscript{a,b}, Sadia Saeed\textsuperscript{d}, Cor Jacobs\textsuperscript{a,b}, Joke van Loenhout\textsuperscript{e}, Dirk de Jong\textsuperscript{f}, Hendrik G. Stunnenberg\textsuperscript{d}, Ramnik J. Xavier\textsuperscript{g,h}, Jos W. M. van der Meer\textsuperscript{a,b}, Reinout van Crevel\textsuperscript{a,b}, and Mihai G. Netea\textsuperscript{a,b,2}

**Figure A**

Survival rate (%) against days post *C. albicans* infection for SCID mice vaccinated with PBS or BCG vaccine.
Hospitalisation results by type of infection

By Sørup, S. et al. (unpublished data)

IRR: MMR vs. DT-aP-IPV-Hib3

- All
- Upper respiratory
- Lower respiratory
- Gastrointestinal
- Other

Estimate 95%-confidence interval
• **EZ high-titre MV** was fully protective against measles => negative non-specific effect (the problem was DTP after MV)

• **Two-dose standard MV** at 4½ and 9 mo was fully protective against measles => beneficial non-specific effect
BCG LBW RCT: Visited at 2 and 6 months

Accumulated mortality curves for DTP vaccinated at 2 months of age and not DTP vaccinated children

<table>
<thead>
<tr>
<th>DTP/noDTP</th>
<th>MRR crude</th>
<th>MRR adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls</td>
<td>2.5 (0.9-6.5)</td>
<td>5.7 (2.1-16)</td>
</tr>
<tr>
<td>Boys</td>
<td>0.5 (0.2-1.2)</td>
<td>1.3 (0.5-3.1)</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td>2.6 (1.4-5.1)</td>
</tr>
</tbody>
</table>
Challenge to our understanding: This makes no sense!

F/M mortality ratio
Measles-vaccinated

F/M mortality ratio
DTP-vaccinated

Modulation of the immune system?
Vitamin A supplementation at birth and infant mortality by sex

Normal-birth-weight:

- **Boys**: MRR=0.8 (0.6-1.3)
- **Girls**: MRR=1.4 (0.9-2.1)

Meta-estimates of the two RCTs
- Boys: 0.80 (0.58-1.09)
- Girls: 1.41 (1.04-1.90)

P for interaction=0.10

Low-birth-weight:

- **Boys**: MRR=0.7 (0.5-1.2)
- **Girls**: MRR=1.4 (0.9-2.2)

P=0.04 for interaction
Live vaccines are good – what happens when removed?
Vaccinia after smallpox eradication in Guinea-Bissau

Mortality rate ratio for Scar/no scar:
- Study I (1998-2002) 0.60 (0.4-0.9); F 0.51 (0.3-0.8); M 0.72 (0.4-1.2)
- Study II (2003-5) 0.22 (0.1-0.6); F 0.19 (0.1-0.6); M 0.40 (0.0-3.7)

Protection against HIV for scar/no scar: Female: 46% (0-71%)
Live vaccines are good - what happens when removed?

Vaccinia after smallpox eradication in Denmark

Smallpox and BCG phased out between 1965-1976 in Denmark
We used Copenhagen school health cards with information on vaccinations to link with Danish health registers

BCG
BCG reduced lymphomas with 51%(7-74%)

Vaccine 2009

Smallpox vaccine
Asthma reduced with 45% (0-70%) - J Allergy Clin Imm 2003
Hospitalisation for inf diseases reduced with 16% (2-28%) IJE 2011

BCG and smallpox vaccine
Reduced the risk of hospitalization for HIV-infection by 65% (12-86%)
New trial of Early MV Bissau: 2011-12
Consultations/hospitalisation rate at paediatric ward

<table>
<thead>
<tr>
<th>Incidence between 4 and 9 months</th>
<th>Rate ratio</th>
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</thead>
<tbody>
<tr>
<td>MV at 4 mo (N=701)</td>
<td>4.6% (32/701)</td>
</tr>
<tr>
<td>Controls (N=350)</td>
<td>9.4% (33/350)</td>
</tr>
</tbody>
</table>
Vaccinations and child survival: Where we are now!

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

INDEPTH Network
Associated: Vadu
Interested: Rufiji; Niakhar; Kisumu

Chakaria
Nairobi
Kintampo

Navrongo
Nouna
Bandim

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