WG: Vaccinations and child survival

Focus:
Monitoring childhood interventions including routine services and campaigns

=> To find possible changes in policy

Why is that necessary?

Paradox:
All interventions justified by their impact on mortality but the impact on mortality has not been studied
Current paradigm in Global Health: **Specific solutions**

- Prevention of specific diseases (malaria, rotavirus, measles etc) and deficiencies (vitamin A, iron etc)
- Effects assumed to be good and proportional to the burden of disease/deficiency
- Effects assumed to be the same for girls and boys
- Effects assume to be independent

If impact on mortality of childhood interventions is considered a different pattern emerge:
RCT of two doses of Measles Vaccine

Two-dose standard MV at 4½ and 9 mo was fully protective and had beneficial non-specific effect on mortality.
MV at 4.5 months: No Maternal Ab
MV at 4.5 months: Maternal Ab

N=450
60% had MatAb 16>= Mother´s level

Mortality ratio from 4 to 60 mo
MV4mo+MatAb vs MV4mo+No MatAb 0.23 (0.1-0.8)
2 RCTs of BCG at birth to LBW infants

<table>
<thead>
<tr>
<th>Trial</th>
<th>Effect within 3 days</th>
<th>Effect within 1st mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002-2004</td>
<td>0.17 (0.02-1.35)</td>
<td>0.28 (0.06-1.37)</td>
</tr>
<tr>
<td>2004-2009</td>
<td>0.49 (0.21-1.15)</td>
<td>0.55 (0.34-0.89)</td>
</tr>
<tr>
<td>Combined</td>
<td>0.42 (0.19-0.92)</td>
<td>0.52 (0.33-0.82)</td>
</tr>
</tbody>
</table>

Due to prevention of neonatal sepsis and respiratory infections
Nothing to do with prevention of TB
2011: Some very 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
Vaccinations and child survival:

These effects may be hard to believe!

But the current paradigm is contradicted

- High-titre MV 2-fold increased mortality for girls
- RCT of BCG 45% reduction in neonatal mortality
- RCT of BCG revaccination after DTP booster 3-fold reduction
- RCT of MV at 4+9 months 50% reduction in mortality between 4 mo and 3 years of age
- RCT: Vitamin A interact negatively with DTP in Bissau and Ghana
- RCT Vitamin A with vaccines has sex-differential effects

This is a huge opportunity for INDEPTH – we are the only ones who can measure “real life” effects for current interventions and all the new vaccines in the pipeline
Vaccinations and child survival: What is required?

**Better data** on vaccination and other inventions
- Few sites have regular data on routine interventions and campaigns
- Data have often been analysed wrongly => we need better analytical methods

**Young scientists** at the centres who can collect and analyse such data

**Develop generalisations** and make them believable and inevitable for *policy change*

=> These needs have defined the WG agenda
Vaccinations and child survival:
I: Research training network

PhD proposal to Danida: Monitoring the impact of childhood interventions on child survival and morbidity (Ballabgarh, Navrongo, Nouna, Nairobi, Kintampo, Bandim)

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

Common data collection methodology: Improve routine data collection on vaccinations => to facilitate observational studies and decide on priority trials

Money from September 2010.
First workshop held in February 2011 in Bissau
Data collection is ongoing
Site visits
Vaccinations and child survival: II. Multicentre study

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

Conduct a multicentre trial of early measles vaccination at 4 months

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

First consortium meeting in Navrongo in April 2011

Trial protocol under development
Vaccinations and child survival

III. Analysis of existing data 2007-2011
- Farafenni => Routine vaccinations and child mortality (Vaccine 2007)
- Navrongo => Vaccines and vitamin A (Am J Clin Nut 2009)
- Vadu: Siddhi: Non-specific and sex-differential effects of vaccinations on child survival in rural western India (submitted)
- Navrongo: Paul Welaga: Non-specific of routine vaccinations: testing the hypothesis with data from Navrongo (to be submitted)
- Draft: cross site paper: The impact of nutritional status on time to vaccination (Vadu, Bissau, Malawi)
- Data from Matlab and Rufiji has also been discussed
Analysis from Farafenni (Vaccine 2007)

Same changes in relative female-male mortality as in Bissau
DTP age (3-8 months) – higher female than male mortality
MV age (9-17 months) – lower female than male mortality

These observations led to RCT of early MV
Global impact

- Bandim and Niakhar: high-titre measles vaccine => increased female mortality – withdrawn by WHO 1992

Current topics:

- Bandim, Nouna, Navrongo: Early MV in RCT

Potential topics

- Early BCG
- Not give DTP after MV
- Not give vitamin A with DTP
- Consequences of eradication
WG 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

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: Chakaria
Interested: Rufiji, Vadu, Kisumu

Ballabgarh
Nairobi
Kintampo
Navrongo
Nouna
Bandim
WG Vaccinations and child survival: Where are we now?

I. Monitoring childhood interventions on child survival. DANIDA research training proposal

- Ballabgarh
- Nairobi
- Kintampo

II. Optimising the impact and cost-effectiveness of child health intervention programmes for vaccines and micronutrients in low-income countries. EU-funding

- Navrongo
- Nouna
- Bandim

III. Stimulate research in child interventions

INDEPTH Network

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- Interested: Rufiji, Vadu, Kisumu
WG: Vaccinations and child survival:

The area questions many current assumptions:

*Specific solutions vs Immunity as a learning system*

It has huge potential for child survival with both beneficial and negative effects:

– MV has beneficial effects. When measles is eradication and vaccinations are reduced child mortality will increase again.

More INDEPTH centres should pursue this area
Non-specific effects of vaccine on child survival

Real life?
Before-after measles vaccination:
Annual mortality rates in African community studies in the 1970s and 1980s

Measles is not 50% of deaths – Why this effect of Measles vaccine? Does not fit current concepts => a beneficial non-specific effect
Vitamin A and early measles vaccination: Morality between 4 and 36 months after measles vaccination at 4 months

<table>
<thead>
<tr>
<th>Deaths/N</th>
<th>Vitamin A at birth</th>
<th>Placebo</th>
<th>Mortality rate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td>20/526</td>
<td>4/350</td>
<td>3.33 (1.2-9.7)</td>
</tr>
<tr>
<td>Girls</td>
<td>13/496</td>
<td>5/329</td>
<td>1.72 (0.6-4.8)</td>
</tr>
<tr>
<td>All</td>
<td>33/1022</td>
<td>9/679</td>
<td>2.44 (1.2-5.1)</td>
</tr>
</tbody>
</table>
Beneficial nonspecific effects:
Early MV at 4+9 mo vs MV at 9 mo

<table>
<thead>
<tr>
<th>Morality rate between 4 and 36 months (deaths/pyrs)</th>
<th>Mortality rate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV at 4 + 9 months</td>
<td>MV at 9 months</td>
</tr>
<tr>
<td>Boys</td>
<td></td>
</tr>
<tr>
<td>1.0 (12/1254)</td>
<td>1.7 (40/2300)</td>
</tr>
<tr>
<td>0.56 (0.29-1.06)</td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td></td>
</tr>
<tr>
<td>1.1 (13/1199)</td>
<td>2.3 (56/2402)</td>
</tr>
<tr>
<td>0.47 (0.26-0.86)</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td></td>
</tr>
<tr>
<td>1.0 (25/2453)</td>
<td>2.0 (96/4703)</td>
</tr>
<tr>
<td>0.50 (0.32-0.78)</td>
<td></td>
</tr>
</tbody>
</table>

Only 10% due to prevention of measles infection; censoring for measles the MRR is 0.55 (0.35-0.87)
Vaccinations and child survival:
Campaigns for a cohort born 2003-6

- BCG vaccination for all children born at the national hospital since 2002
- Vitamin A and missing vaccination campaign in 2003
- OPV campaigns in 2004 and 2005
- Measles vaccination campaign in 2006 for all children aged 6 months to 15 years
- Measles vaccination campaign in 2009 for all children aged 9 months to 5 years of age
- Bed net distribution 2006 and 2007
- Bed net impregnation 2006 and 2007
- De-worming every year 2006-2009
WG: Vaccinations and child survival

DANIDA application for 3 mill $ for this network

Response: Science okay – you can get 2 mill if you can get the last mill elsewhere

We are trying to apply to EDTCP together with Heidelberg

If this is not feasible we have to have an alternative ”low cost” solution
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=0.01

Low-birth-weight:

MRR=0.7 (0.5-1.2)

MRR=1.4 (0.9-2.2)

P=0.04 for interaction
MV at 4+9mo vs No vac(DTP3)+MV at 9mo by Vitamin A-at-birth status

Vitamin A may have a fundamental impact on the NSEs
WG: Vaccinations and child survival

- What has happened 2007-2009
  - Centre visits – Nouna; Kilifi; Navrongo; Ballabgarh, Vadu, Rufiji
  - 2008: Small grants from Indepth/DANIDA =>
  - April 2008: Workshop on non-specific effects of vaccines in London (organised by Peter Smith). Resulted in 3 papers =>
    - Data Collection (TMIH)
    - Analytical issues (TMIH)
    - Potential randomised trials of non-specific effects (PIDJ)
  - 2009 Applications to DANIDA, EDCTP, EU-FP7
  - 2010: Danida – 1.3 mill € for research training network and EU-FP7 possibly 3 mill € for multisite study; EDCTP: 0
Before-after measles vaccination (MV):
Annual mortality rates in African community studies

Bissau: MV at 6 mo introduced 1979 - 3-fold reduction
Measles infection may have caused 10-20% of deaths!
=> A beneficial effect unrelated to measles prevention
The VAS effect differed in children with (N=6,656) and without (N=5,066) a health card – due to differential effect of VAS in girls (P<0.01)

Benn et al, Am J Clin Nut 2009