Measles vaccination in presence of maternal measles antibodies confers Nonspecific beneficial effects on child survival

Christine Stabell Benn, Cesario Martins & Peter Aaby
Bandim Health Project, Guinea-Bissau
MV at 4+9mo vs MV at 9mo
(3402 infants with no Vitamin A at birth)

Mortality rate

Reduction in overall mortality:
Two MV at 4½ and 9 mo: 50% (22-68) (F: 53%(14-74); M: 44%)
Measles inf censored 45% (14-65)

BMJ 2010
Development of hypothesis

• Zinkernagel: One should meet the pathogens in the presence of maternal antibodies

• Beneficial to receive measles vaccine in the presence of maternal measles antibodies?
Mortality ratio from 4 to 60 mo
MV4mo+MatAb vs MV4mo+No MatAb
Effect after 2nd MV (9-60 mo)  
0.23 (0.1–0.8)  
0.26 (0.1–0.9)
Controls MV at 4.5 months: No Maternal Ab
MV at 4.5 months: Maternal Ab

Accumulated mortality (%)

Age in Years

Accumulated mortality (%) versus Age in Years
### MV in presence or absence of MatAb: Effect on survival in RCTs in Guinea-Bissau

<table>
<thead>
<tr>
<th>Study</th>
<th>Period</th>
<th>Age MV</th>
<th>MatAb+ (deaths/pyrs)</th>
<th>No MatAb (deaths/pyrs)</th>
<th>Mortality Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTP not given after MV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-dose MV</td>
<td>2003-09</td>
<td>4½ mo</td>
<td>3/908</td>
<td>11/760</td>
<td>0.23 (0.1-0.8)</td>
</tr>
<tr>
<td>DTP given with or after MV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium-titre EZ MV</td>
<td>1985-90</td>
<td>4 mo</td>
<td>17/568</td>
<td>15/266</td>
<td>0.53 (0.3-1.1)</td>
</tr>
<tr>
<td>2-dose MV</td>
<td>1993-98</td>
<td>6 mo</td>
<td>0/75</td>
<td>11/339</td>
<td>0 (0-2.0)</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.45 (0.2-0.9)</td>
</tr>
</tbody>
</table>
Reduction in mortality (%) associated with measles vaccination (MV):
Comparing MV before 12 months versus MV unvaccinated children

MV before median age of MV is better for child survival than later MV: Mortality ratio <median/>median: 0.49(0.3-0.8)
(No difference among controls)

MatAb likely explanation
Biological mechanisms?

- Animal studies: vaccines induce heterologous protection against unrelated antigens through cross-reaction of T-cell epitopes
- The beneficial non-specific effects of measles vaccine could be caused by heterologous immunity due to cross-reactive epitopes

- In the presence of maternal antibodies, the child may respond more to subdominant epitopes, leading to a more diverse T- and B-cell repertoire and increased heterologous protection against other pathogens

- Furthermore, maternal antibody-antigen complexes are powerful immunogens, and this could result in enhanced T-cell responses in infants immunised in the presence rather than in the absence of maternal antibodies
Maternal measles antibodies

Child age

2  4  6  8  10  12 months
Specific protection against measles infection

Maternal measles antibodies

Child age

2             4               6                8                10              12 months
Specific protection against measles infection

Maternal measles antibodies

Child age

Assumed survival benefit from prevention of measles infection

Latin America in 1996: age of MV increased from 9 to 12 months
SAGE recommends to increase MV from 9 to 12 months with improved control
Maternal measles antibodies

Vaccine efficacy against measles infection

Observed survival

Benefit (VED)

Child age

2 4 6 8 10 12 months

Assumed survival benefit from prevention of measles infection

Eradication of measles will increase child mortality?

Latin America in 1996: age of MV increased from 9 to 12 months
SAGE recommends to increase MV from 9 to 12 months with improved Measles control
Prediction: Infants will be deprived of beneficial effects of MV
=> Child mortality will increase
RCTs of two doses of measles vaccine vs standard policy of one dose at 9 month

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up period</th>
<th>Mortality rate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudan, 1989-92 Vaccine 2007</td>
<td>5-36 mo</td>
<td>0.60 (0.3-1.4)</td>
</tr>
<tr>
<td>Bissau, 1993-95 IJE 2003</td>
<td>6-18 mo</td>
<td>0.66 (0.2-2.3)</td>
</tr>
<tr>
<td>Bissau, 2003-09 BMJ2010</td>
<td>4½-36 mo</td>
<td>0.50 (0.3-0.8)</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td>0.53 (0.36-0.77)</td>
</tr>
<tr>
<td>Observational study campaigns BMJ 1993</td>
<td>9-60 mo</td>
<td>0.41 (0.2-0.9)</td>
</tr>
</tbody>
</table>

9-60 mo 4-8 vs 9-11 mo
Conclusions and implications

- The current MV programme assumes that the efficacy of MV against measles infection and the effect on survival increases with age as maternal antibodies wane.
- However, in total contradiction of these assumptions,
  - the beneficial effect of MV was found only among children who had maternal antibodies at the time of vaccination
  - MV at 4.5 months of age in the presence of maternal antibody reduced all-cause mortality 4-fold between 4.5 months and 5 years of age compared with controls who received the recommended MV at 9 months of age
- Implications:
  - we would need to understand how maternal antibodies generate a beneficial immune profile following early measles vaccination
  - current MV policies should be reconsidered; we should vaccinate earlier rather than later
Specific protection against measles infection

Observed general survival benefit (VED)

Assumed survival benefit from prevention of measles infection

Maternal measles antibodies

Child age

2  4  6  8  10  12 months
Table 1. Mortality between 4.5 and 60 months of age in relation to the presence of maternal HAI antibodies at the time of measles vaccination (4.5 months of age)

<table>
<thead>
<tr>
<th>Maternal antibody concentration</th>
<th>Deaths/children having lower level than mother</th>
<th>Deaths/children having same or higher level than mother</th>
<th>Deaths/all children</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 31.25 miU (minimum detectable level)</td>
<td>11/201</td>
<td>11/201</td>
<td></td>
</tr>
<tr>
<td>31.25 miU*</td>
<td>0/84</td>
<td>0/1</td>
<td>0/85</td>
</tr>
<tr>
<td>62.50 miU*</td>
<td>1/44</td>
<td>1/44</td>
<td></td>
</tr>
<tr>
<td>125</td>
<td>1/45</td>
<td>0/1</td>
<td>1/46</td>
</tr>
<tr>
<td>250</td>
<td>0/31</td>
<td>1/1</td>
<td>1/32</td>
</tr>
<tr>
<td>500</td>
<td>0/14</td>
<td>0/1</td>
<td>0/15</td>
</tr>
<tr>
<td>1000</td>
<td>1/9</td>
<td>0/2</td>
<td>1/11</td>
</tr>
<tr>
<td>2000</td>
<td>0/4</td>
<td>0/3</td>
<td>0/7</td>
</tr>
<tr>
<td>4000</td>
<td>0/2</td>
<td>0/4</td>
<td>0/6</td>
</tr>
<tr>
<td>8000</td>
<td></td>
<td>0/2</td>
<td>0/2</td>
</tr>
<tr>
<td>16000</td>
<td></td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>31.25-16000 miU</td>
<td>3/233</td>
<td>1/16</td>
<td>4/249</td>
</tr>
</tbody>
</table>

Note: Titres of <125 miU are usually considered non-protective; antibodies were measured with the HAI (haemagglutination inhibition) test.

MRR for antibody+MV/no antibody+MV: 0.23 (0.06-0.82)