Randomised trial to test the non-specific effects of standard measles vaccine at 4½ and 9 months of age: General reduction in childhood mortality

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Introduction of measles vaccination in African communities: Annual mortality before and after

Measles not more than 10-20% of deaths. Reduction in mortality not due to prevention of acute and long-term effects of measles infection.

Measles vaccine (MV) - beneficial non-specific effects (NSE)
Introduction of DTP:
Rural areas of Guinea-Bissau 1984-87

Diphtheria-Tetanus-Pertussis has negative effects for girls
High-titre measles vaccine: 2-fold higher female mortality

Lessons from high-titre measles vaccine (HTMV) trials:
- EZ HTMV was fully protective against measles => negative non-specific effect
- Sex-differential effect
- Public health effects: 35% excess mortality from 4 to 60 months => at least ½ mill annual deaths in Africa

WHO introduced HTMV 1989 and withdrew it in 1992 =>
Interpretation: Too much of a good thing => Major donors: Money for new vaccines!

=> We looked for important NSEs of other vaccines
What can be done to reduce the negative effect of DTP?

Increased female mortality in the age groups of DTP

=> Change the immunological profile with a live vaccine

=> RCT: Early Measles Vaccine at 4½ m
Testing non-specific effects of MV

- Recruitment 2003-2007 – Follow-up to 2009
- 6,600 randomised to A) Edmonston-Zagreb (EZ) at 4½+9 mo, or B+C) no vaccine at 4½ mo and EZ MV or Schwarz MV at 9 mo
- DTP3 four weeks before enrolment – to prevent the problem of DTP after MV
- Study designed to test a 25% difference in mortality

Comparisons
- MV versus DTP3 between 4 and 8 months
- MV at 4+9 mo versus MV at 9 mo between 9-36 mo
Procedures

- Newborns were identified in database of Bandim HDSS
- Before inclusion, mothers reminded to complete the OPV/DTP vaccination schedule at 6, 10, and 14 wks
- The formal inclusion in the study was carried out at 4½ months of age
Measles epidemic in Bissau, 2003/2004

Vaccine efficacy of early MV
- Definite measles: 94% (77-99)
- Hospitalisation: 100% (46-100)
- Measles death: 100% (-42-100)
**MV at 4½+9mo vs No vac(DTP3)+MV at 9mo**

Follow to 3 yrs for all children (2003-2009)

Mortality rate

<table>
<thead>
<tr>
<th>Age Group</th>
<th>MV 4+9 mo</th>
<th>DTP3+MV 9 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-8 mo</td>
<td>0.67(0.4-1.2)</td>
<td></td>
</tr>
<tr>
<td>9-36 mo</td>
<td>0.71(0.5-1.0)</td>
<td>0.69(0.5-0.9)</td>
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<tr>
<td>4-36 mo</td>
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</tbody>
</table>

Two MVs at 4 and 9 mo: 31% (6-49%)  (F: 41 % (9-62); M: 18%)

Measles inf censored: 26% (0-46%)

(NB not against unvaccinated)
MV at 4+9mo vs No vac(DTP3)+MV at 9mo by Vitamin A-at-birth status

Mortality rate

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<tr>
<td></td>
<td>0.98(0.6-1.5)</td>
<td>0.34(0.2-0.7)</td>
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</tbody>
</table>

P=0.012

Vitamin A may have a fundamental impact on the NSEs => Only those who did not receive VAS-at-birth
MV at 4+9mo vs No vac(DTP3)+MV at 9mo (3402 infants with no Vitamin A at birth)

Reduction in overall mortality:
Two MV at 4½ and 9 mo: 49% (22-68) (F: 53%(14-74); M: 44%)
Measles inf censored 45% (14-65)
Children born before June 2004

- Two-dose MV
- One-dose MV

MRR = 0.48 (0.26-0.87)
P-value = 0.02

Number at risk:
- Two-dose: 405, 377, 334
- One-dose: 750, 660, 594

Children born after June 2004

- Two-dose MV
- One-dose MV

MRR = 0.53 (0.28-1.00)
P-value = 0.05

Number at risk:
- Two-dose: 599, 541, 485
- One-dose: 1184, 1062, 940
Testing non-specific effects of early measles vaccination:

Conclusions

Key features
- Low maternal antibody levels
- Edmonston Zagreb (EZ) measles vaccine
- All had DTP3 before measles vaccine

Conclusions
- EZ at 4½ mo is protective against measles infection
- MV affects non-measles morbidity - 49% (15-69) reduction in hospitalisations for girls – 16% for boys
- MV vs DTP3 between 4-8 mo: 64% (8-86) reduction in mortality
- MV at 4½+9 mo vs MV at 9 mo between 9-36 mo: 43% (7-66)
Non-specific effects (NSE) of standard MV at 4½ and 9 months of age:

General reduction in childhood mortality

- Vaccines stimulate the immune system affecting susceptibility
- The NSE are often more important than specific effects
- Vaccination programmes should take the NSE into consideration: age at vaccination, number of vaccinations, sequence of vaccinations
- Reconsider assumptions –
  - Focus: specific diseases or immune deviations
  - Effects may differ for boys and girls
  - Interventions interact
- INDEPTH in a unique position to pursue these problems
- ➞ EU is (hopefully) going to fund a multicentre trial of early MV
HTMV and DTP?

**No DTP after HTMV**

- **Senegal HT**
- **Senegal routine**
- **Bissau**
- **Gambia**
- **Sudan**
- **Congo**

**DTP/IPV after HTMV**

- **Senegal HT**
- **Senegal Routine**
- **Bissau**
- **Gambia**
- **Sudan**

F/M ratio: 0.96 (0.7-1.3)  
F/M ratio: 1.93 (1.3-2.8)

Not RCT – but this ”proves” a causal biological process

HTMV withdrawn for the wrong reason