Non-specific effects of routine immunisations in Denmark

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Non-specific effects of vaccines

Health effects not related to the protection against the targeted diseases
Non-specific effects of vaccines: Hypotheses generated in low-income countries

• Most recent vaccine
  – *Live* vaccines are associated with decreased mortality
  – *Inactivated* vaccines are associated with increased childhood mortality
  – Simultaneous administration of *live* and *inactivated* vaccines are associated with increased childhood mortality

SAGE review of non-specific effects of vaccines

- **Live** Bacille Calmette-Guérin (BCG) and **live** measles containing vaccines: “The review suggested possible beneficial effects on all-cause mortality”

- **Inactivated** diphtheria, tetanus and pertussis vaccine (DTP): “The available data neither exclude nor confirm the possibility of beneficial or deleterious non-specific effects”

- Further research is warranted

Wkly Epidemiol Rec 2014, p. 221-36
Objective

To examine the potential non-specific effects of routine childhood vaccines on infectious disease hospital admissions among Danish Children.
# Danish vaccination schedule

**Jan 1997 - Oct 2007**

<table>
<thead>
<tr>
<th>Age in months</th>
<th>Penta</th>
<th>Penta</th>
<th>Penta</th>
<th>MMR</th>
<th>(OPV)</th>
<th>(OPV)</th>
<th>(OPV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>5</td>
<td>12</td>
<td>15</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
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<tr>
<td><strong>Age in years</strong></td>
<td></td>
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</tbody>
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Penta = Diphtheria, tetanus, pertussis, polio, and *Haemophilus influenzae* type b  
MMR = Measles, mumps, and rubella  
OPV = Oral polio vaccine
DESIGN
Design: Nationwide retrospective cohort studies

**Vaccinations**

**Hospital admissions due to infections**

**Admission with laboratory-confirmed RSV**

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**“Vulnerability” factors**
- Age, maternal smoking during pregnancy, birth weight, prematurity, caesarean section, chronic diseases, previous admissions with infections, recent admissions

**Socioeconomic factors**
- Maternal age, single parenthood, other children in the household, parental origin, household income and maternal education

**External factors**
- Season and calendar year
The importance of age

Distribution of vaccinations

Admissions by age
Statistical analysis

• Cox proportional hazards model
  – Time scale: age

[Diagram showing age scale from 12 to 15 months with highlighted time points]
STUDIES OF MMR AND PENTA
MMR vs. Penta3

• Birth cohort 1997-2006
• Penta2 before 11 months of age
• ~ 480,000 children
• Follow-up to 2 years of age (or other vaccines (OPV))

Sorup et al. JAMA 2014
Results: All-cause infections

456,043 children
42,054 admissions due to infections

Penta2 before 11 months of age → Penta3 (124/1000) → MMR (89/1000)

0.86 (0.84-0.88)

Sorup et al. JAMA 2014
Results: All-cause infections

- **Penta2 before 11 months of age**
- **Penta3** (124/1000)
- **MMR** (99/1000)
- **Penta3** (128/1000)
- **MMR** (89/1000)

456,043 children
42,054 admissions due to infections

19,219 children
1153 admissions

Sources:
Sorup et al. JAMA 2014
Results: Type of infection

IRR_{adj} : MMR vs. Penta3

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

Sorup et al. JAMA 2014
MMR vs. Penta3 on RSV admissions

• Birth cohort 1997-2002
• Penta1, 2 and 3 at recommended ages (3, 5, and 12 months, respectively)
• ~170,000 children
• Follow-up to 2 years of age (or other vaccines (OPV))
Results: Type of infection including RSV

IRR\textsubscript{adj}: MMR vs. Penta3

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

Sorup et al. JAMA 2014; Sorup et al. Vaccine (in press)
MMR + Penta vs. MMR

- Birth cohort 1997-2006
- Have received at least one dose of either Penta or MMR
- ~ 560,000 children
- Follow-up to 4 years of age (or other vaccines (OPV))
Results: All-cause infections

- **MMR**
  - 52,075 admissions
  - 910,702 person years
  - (57/1000)

- **MMR + Penta**
  - 862 admissions
  - 12,591 person years
  - (68/1000)

Relative Risk: 1.07 (1.00-1.15)

Sorup et al. (under review)
Results: Type of infection

IRR$_{adj}$: MMR+Penta vs. MMR

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

Sorup et al. (under review)
STUDY OF OPV
MMR and Penta3 vs. OPV

- Birth cohort 1997-1999
- Have received Penta3 before 2 years of age
- ~137,000 children
- Follow-up to 3 years of age

Sorup et al. (unpublished)
Results: Type of infection

IRR$_{adj}$ compared with OPV

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

Sorup et al. (unpublished)
CONCLUSIONS
• MMR as the most recent vaccine is associated with 14% (12%-16%) lower rate of infectious disease admission compared with Penta3
  – Stronger for
    • lower respiratory infections: 20% (16%-24%)
    • Including laboratory-verified RSV: 22% (7%-34%)

• Simultaneous administration of MMR and Penta is associated with 27% (13%-42%) higher rate of admission for lower respiratory infections compared with MMR alone
• Penta3 is associated with 37% (15%-64%) higher rate of admission for lower respiratory infections compared with OPV

• No difference between MMR and OPV
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Thank you! Any questions?

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