Non-specific effects of vaccines

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HISTORY OF NON-SPECIFIC EFFECTS OF VACCINES
Child mortality, Guinea-Bissau, West Africa

Mortality, 6-35 months of age

Map by Wikimedia commons

Aaby et al. J Infect 1984
Measles vaccine introduction and child mortality

- Guinea-Bissau: 6-35 months
- Congo: 9-34 months
- Senegal: 9-23 months
- Senegal: 9-59 months
- India: 12-59 months

Bandim Health Project: Study setting

Urban: Follows 102,000 individuals in 6 districts

Rural: Follows 25,000 women and their children in 180 village clusters
Pregnancy lists

Once a month, all houses in the study area are visited:

• New pregnancies
• Status of already registered pregnancies
• Register new born children
Child lists

Every 3rd month:

- Vital status
- Vaccines
- Nutritional status
- Infections
- Hospitalizations
Bandim Health Project: Observational studies and randomized trials of non-specific effects of vaccines
Randomised trial of Measles vaccine

Recommended vaccination schedule

DTP
6,10,14 weeks

MV
9 months

Trial arm

DTP
6,10,14 weeks

MV
4.5 months

MV
9 months

Aaby et al. BMJ 2010
Randomised trial of Measles vaccine: Mortality

Mortality rate per 100 person years

- All children: N=6417
- Measles vaccine
- No vaccine (DTP3)

MRR=0.67 (0.38-1.19)

Aaby et al. BMJ 2010
Randomised trial of Measles vaccine: Admissions

Admission rate per 100 person years

AHRR=0.70 (0.52-0.95)

All children N=6417

- Measles vaccine
- No vaccine (DTP3)

Martins et al. J Infect Dis 2014
Randomised trial of Measles vaccine: Admissions

Admission rate per 100 person years

AHRR=0.30 (0.13-0.70)  AHRR=0.73 (0.34-1.28)

Females N=1714
Males N=1688

Measles vaccine  No vaccine (DTP3)

Martins et al. J Infect Dis 2014
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

• Sex-differential effects

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
NON-SPECIFIC EFFECTS OF VACCINES IN DENMARK
Objective

To examine the potential non-specific effects of the *Live* measles-mumps-rubella vaccine on infectious disease hospital admissions among Danish Children.
Danish vaccination schedule

Jan 1997- Oct 2007

Penta Penta Penta MMR (OPV) (OPV) (OPV)

3 5 12 15 2 3 4

Age in months Age in years

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**

**“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

Age in months

Penta  MMR

Age in months
Statistical analysis

• Cox proportional hazards model
  – Time scale: age
Statistical analysis

• Cox proportional hazards model
  – Time scale: age
  – Adjustment for potential confounders
  – Adjusted incidence rate ratios (95% CI)
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

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

- Penta2 before 11 months of age
- Penta3 (124/1000) → MMR (89/1000): 0.86 (0.84-0.88)
  - 456,043 children
  - 42,054 admissions due to infections
- MMR (99/1000) → Penta3 (128/1000): 1.62 (1.28-2.05)
  - 19,219 children
  - 1153 admissions

Sorup et al. JAMA 2014
Results: By sex

Number of admissions per 1000 person years

- Male: 0.85 (0.83-0.88)
- Female: 0.87 (0.84-0.90)

P interaction: 0.26

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
Results: Public Health Impact

• Numbers needed to vaccinate
  – 201 (159-272) children should be vaccinated with MMR before 16 months of age to avoid one admission with any infection between age 16 months and 2 years

Sorup et al. JAMA 2014
Public Health Impact: Number of admissions avoided

• Assumptions
  – MMR coverage at 16 months of age: 50%
  – One birth cohort in Denmark: 65,000 children
    → 32,500 children vaccinated timely with MMR

• Number of admissions avoided
  \[
  \frac{32,500}{201} \approx 162 \text{ (119-204)}
  \]
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))

Sorup et al. Vaccine 2015 30
Results: RSV-admissions

Penta1, 2, and 3 at recommended ages

Penta3 (9/1000)

0.78 (0.66-0.93)

MMR (6/1000)

168,511 children
888 admissions

Sorup et al. Vaccine 2015
Results: By sex

Number of admissions related to RSV per 1000 person years

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penta 3</td>
<td>0.74 (0.60-0.92)</td>
<td>0.84 (0.66-1.06)</td>
</tr>
<tr>
<td>MMR</td>
<td>6.00</td>
<td>6.00</td>
</tr>
</tbody>
</table>

P interaction 0.42

Sorup et al. Vaccine 2015
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 (57/1000)  
52,075 admissions  
910,702 person years

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

1.07 (1.00-1.15)

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

IRR\textsubscript{adj}: MMR+Penta vs. MMR

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

Sorup et al. (submitted)
Results: By sex

Number of admissions with lower respiratory infections per 1000 person years

Male: 1.26 (1.08-1.47)
Female: 1.28 (1.07-1.53)

Sorup et al. (submitted)
Main message:
**MMR** is good

**MMR** is associated with lower rate of infectious disease admission, particularly for lower respiratory infections
Real effect?

• Design features
  – Selected population
  – Reversed sequence of vaccines
  – Adjustment for multiple confounders

• Unmeasured confounders?
Biological mechanisms? Specific effects of a vaccine

- Innate immune cell
- Naive cell
- Memory cell
- Pathogen
- Expansion
- Clearance
Biological mechanisms?
Non-specific effects of a vaccine

- Cross-reactive memory T-cell
  - Th1 memory
  - Th2 memory
  - Faster pathogen clearance
  - Immunopathology
  - Slower pathogen clearance
  - Atopic diseases?

- Naive T-cell
  - Unrelated pathogen
  - Rapid activation of altered antigen presenting cells
  - Pro-inflammatory cytokines
  - Faster pathogen clearance

- Innate immune cell
  - Reprogramming

- Trained innate immune cell
  - Benn et al. Trends Immunol 2013
CONCLUSIONS
International
• Focus on non-specific effects of vaccines
  – Possible beneficial effects of live vaccines
• Further research is warranted

Denmark
• 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%)
Denmark

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

• Similar non-specific effects of vaccines for females and males

• Further research is warranted
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Thank you! Any questions?

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