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“A vaccine is a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism.... The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters” (Wikipedia)

“With the exception of safe water, no other modality, not even antibiotics, has had such a major effect on mortality reduction and population growth” (Plotkin)
Current consensus

• Vaccines are always beneficial

• We know what they do: protect against the target disease

• Two types of research are needed
  – Programmatic research into how we make sure that all children are vaccinated
  – Research into developing the vaccines we don’t have
What is the evidence that vaccines have specific effects?

- Antibody titres
- Cellular immunity?
- Clinical protection against target disease
- Overall mortality?
What is the evidence that vaccines have only specific effects?

NONE
Bandim Health Project

A platform for testing real-life effects of health interventions

- **Guinea-Bissau**: Bissau City
- **Rural Guinea-Bissau**: > 100,000 individuals in 180 villages
BCG vaccine
BCG-at-birth to LBW children: 2004-08

Mortality rate

MRR=0.55(0.4-0.9)
MRR=0.83(0.6-1.1)

- 45% reduction in neonatal mortality –
- Reduction in neonatal sepsis and respiratory infections
- Not prevention of TB => Beneficial non-specific effects of BCG

J Infect Dis 2011
BCG biological mechanism?

Bacille Calmette-Guérin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes

Johanneke Kleinnijenhuis, Jessica Quintin, Frank Preijers, Leo A. B. Joosten, Daniela C. Ifrim, Sadia Saeed, Cor Jacobs, Joke van Loenhout, Dirk de Jong, Hendrik G. Stunnenberg, Ramnik J. Xavier, Jos W. M. van der Meer, Reinout van Crevel, and Mihai G. Netea

PNAS 2012
Measles vaccine
MV at 4+9 months vs DTP3+MV at 9 months
3402 infants with no vitamin A supplementation at birth

Mortality rate

<table>
<thead>
<tr>
<th>Time</th>
<th>MV 4+9 mo</th>
<th>DTP3+MV 9 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-8 mo</td>
<td>0.33 (0.1-0.9)</td>
<td></td>
</tr>
<tr>
<td>9-36 mo</td>
<td>0.56 (0.3-0.9)</td>
<td>0.50 (0.3-0.8)</td>
</tr>
</tbody>
</table>

Reduction in overall mortality from 4-36 mo:
- Two MV at 4½ and 9 mo → 50% (22-68)
- Measles infection censored → 45% (14-65)
Diphtheria-tetanus-pertussis vaccine
Introduction of DTP: Rural areas 1984-87

Children aged 2-8 mo
Followed 6 mo

Unvaccinated: travelling; sick; days without vaccines

\[ \text{DTP}^- \quad (N=868) \]

\[ \text{DTP}^+ \quad (N=967) \]

\[ \text{DTP}^+ / \text{DTP}^- \quad 1.98 (1.03-3.8) \]

Int J Epidemiol 2004
Turning to Denmark....

Vaccination schedule 1997-2007:

- DTaP-IPV-Hib1: 3 months
- DTaP-IPV-Hib2: 5 months
- DTaP-IPV-Hib3: 12 months
- MMR1: 15 months

Age in months
In 2012-13: 4,300 children enrolled, randomised to BCG or nothing
Main outcomes: infectious diseases, atopic diseases; immunological studies
Conclusion

- Vaccines only tested for their specific effects
- No evidence that they do not have non-specific effects
- New compelling evidence that all vaccines have strong effects on overall mortality which cannot be explained by specific effects – *non-specific effects*
- The immune system is a learning system, which can be modulated by vaccines with strongly beneficial (BCG, measles vaccine) but also sometimes detrimental effects (diphtheria-tetanus-pertussis vaccine)
- The effects are often sex differential, both beneficial and detrimental effects strongest in females
Consequences for Denmark?

- MMR: 15-20% reduction in infectious disease hospitalisations
- Vaccinated mothers – transfer lower antibodies
- Measles vaccine better effect if given in presence of maternal antibodies
- => Lower the age of measles vaccination? Randomised trial?

- Use every opportunity to study changes in vaccination program: introduction of new vaccines (rotavirus vaccine, varicella?), changes in age of vaccination (Norway and Finland just moved MMR from 15 to 12 months of age)

- If MMR has beneficial non-specific effects it would be a strong argument for vaccination
Consequences for Denmark?

- The current vaccination schedule is built on the ”Specific effects paradigm” – the goal being to achieve as high an antibody response as possible

- If vaccines have non-specific effects, and the main goal was to lower overall morbidity rather than just disease-specific morbidity the schedule might look different
Proposed schedule

- BCG?
- DTaP-IPV-Hib1
- DTaP-IPV-Hib2
- MMR1
- MMR2

Age in months:
- 0
- 3
- 5
- 6
- 15