A brief introduction to the non-specific effects of vaccines

Peter Aaby
Bandim Health Project
Disclaimer

- I am not an anti-vaccine person
- I am a great fan of many vaccines
- I believe that these vaccines have been instrumental for the incredible reduction in all-cause mortality in low-income countries during the last 3-4 decades
- But not all vaccines work equally well
OPTIMUNISE is built on a conflict of ideas

Public health interventions focus exclusively on prevention or treatment of specific diseases

OPTIMUNISE argues that vaccines often train the immune system: enhancing or misdirecting it!

In this study: measles vaccine also reduced mortality by 30%

The decline in mortality in LMIC cannot be understood without these beneficial effects. If these effects were taken into consideration in planning of vaccination programmes, child mortality could be further reduced

Martins et al BMJ 2008

Early measles vaccination reduced measles infection with 94%
Good news: Before-after measles vaccine

Annual mortality rate in community studies

>50% reduction - Measles was 10-15% of deaths (WHO)

How is that possible?

=> The idea: The vaccine teaches the immune system to fight other infections

=> It has NON-SPECIFIC EFFECTS
The vaccines were tested for their specific preventive effects but not for overall effects on child survival.

How to test whether a vaccine has non-specific effects?
Live vaccines have beneficial non-specific effects in randomised trials

Vaccines may train the immune system beneficially

<table>
<thead>
<tr>
<th>Randomised Trials</th>
<th>Outcome</th>
<th>Overall reduction in mortality</th>
<th>Nonspecific reduction</th>
<th>Specific disease reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Trials of BCG at birth</td>
<td>Neonatal mortality</td>
<td>38% (17-54%)</td>
<td>38% (17-54%)</td>
<td>0%</td>
</tr>
<tr>
<td>Oral polio vaccine at birth</td>
<td>Infant mortality</td>
<td>32% (0-57%)</td>
<td>32% (0-57%)</td>
<td>0%</td>
</tr>
<tr>
<td>MV at 4+9 vs 9 mo</td>
<td>Mortality 4-36 mo</td>
<td>30% (10-50%)</td>
<td>26% (0-45%)</td>
<td>4%</td>
</tr>
</tbody>
</table>
Ultimate victory in public health is Eradication=> removing a vaccine with beneficial effects?

Smallpox vaccine removed in the 1970s

I. Urban Guinea-Bissau: smallpox vaccination scar associated with 40% (13-59%) lower mortality (Vaccine 2006)

II. Rural Guinea-Bissau: Smallpox vaccination scar associated with 78% (39-92%) lower mortality (PLoS One 2006)

III. Copenhagen 1971-2010: Smallpox vaccination + BCG associated with 46% (19-64%) lower mortality for natural causes of death; no effect for accidents and suicides (Int J Epidemiol 2016)
The Good news on non-specific effects of vaccines

The vaccines with beneficial effects are live vaccines which replicate in the vaccinated individual.
Not all vaccines have beneficial effects: WHO review of non-specific effects of BCG, DTP and Measles Vaccine
Effect on child survival of different vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>ES (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>0.53 (0.40, 0.72)</td>
</tr>
<tr>
<td>DTP</td>
<td>1.38 (0.92, 2.08)</td>
</tr>
<tr>
<td>MCV</td>
<td>0.54 (0.45, 0.65)</td>
</tr>
</tbody>
</table>

WHO recommended Further studies of NSEs
Bad news: High titre measles vaccine WHO-recommended in 1989 associated with 2-fold higher female mortality

5 African studies: 33% excess mortality from 4 mo to 5 years
But the vaccine was protective against measles infection!
And the vaccine made no difference for boys!
DTP has negative effects for all-cause mortality for girls

Vaccines may misdirect the immune system

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Studies</th>
<th>Higher mortality for females vs males among vaccinated children</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTP</td>
<td>16 studies</td>
<td>50% (21-85%)</td>
</tr>
</tbody>
</table>

The effect of DTP for girls explained the higher mortality after high-titre measles vaccine. This vaccine was given so early that nearly all got DTP after measles vaccine and that had a negative effect for girls.
Non-live vaccines may have negative effects for all-cause mortality for girls

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Studies</th>
<th>Relative mortality for female vs male among vaccinated children</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTP</td>
<td>16 studies</td>
<td>50% (21-85%)</td>
</tr>
<tr>
<td>IPV</td>
<td>3 trials</td>
<td>52% (2-128%)</td>
</tr>
<tr>
<td>HBV</td>
<td>1 natural exp.</td>
<td>120% (7-354%)</td>
</tr>
<tr>
<td>Malaria vaccine</td>
<td>2 trials</td>
<td>33% (2-74%)</td>
</tr>
<tr>
<td>Pentavalent vaccine</td>
<td>Health Centre Study</td>
<td>73% (11-74%)</td>
</tr>
</tbody>
</table>
The Good and Bad News on non-specific effects (NSEs) of immune training

Four themes

- Live vaccines have beneficial NSEs
- Non-live vaccines may have negative effects for girls
- Effects often differ for girls and boys
- Sequence of vaccinations may be very important

OPTIMUNISE is use the beneficial effects better and minimise the negative effects