Hepatitis B immune memory in children primed with hexavalent vaccines

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Hexavalent vaccines - 1

- In 2000, Hexavac® and Infanrix Hexa® were licensed in the EU for vaccinating children against hepatitis B, tetanus, diphtheria, pertussis, poliomyelitis and invasive infections caused by Hemophilus influenzae b.
- In 2005, Hexavac was suspended by EMA because of concerns over the immunogenicity of HBsAg contained in this vaccine.

Hexavalent vaccines - 2

- No action was taken over Infanrix Hexa since the immunogenicity of its HB component did not raise equal concern.
- Until suspension, approx 10 million doses of Hexavac were distributed globally.

AIM:
To assess duration of immunity and need for booster in children primed 5 years previously with hexavalent vaccines during their first year of life.

Study design

- Healthy children born to HBsAg negative mothers who received 3 doses of hexavalent vaccines at 3, 5 and 11 m of age.
- Setting: 6 Local Health Units located in northern Italy and at Hospital “Bambino Gesù” – Vatican, Rome.
- Written informed consent.
- Approval by Ethics Committee of the University of Milan.

Flow-chart

- Test for anti-HBc and anti-HBs (titre)
- anti-HBc+
- anti-HBs <10 mIU/ml
- anti-HBs ≥10 mIU/ml
- *HBVaxPro (5 µg) or Engerix B (10 µg)
- randomly assigned to a booster dose of HB monovalent vaccine
- 15–13 days later: anti-HBs (titre)
- Anamnestic response
- No response
- 2 additional doses of vaccine
- STOP
- Immunity
- STOP
**Study population**

1543 children enrolled
- 833 primed with Hexavac
  - 2 excluded anti-HBc +
  - 831 included in the study
- 710 primed with Infanrix
  - 1 excluded anti-HBc +
  - 709 included in the study
- 2 excluded

**Total of children included in the study**
1540

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**Demographic features of children included in the study**

- **Total**: 1540 children
- **Gender**: 47.9% F; 52.1% M
- **Year of birth**: 2001-2003
- **Mean age at enrollment**: 5.6 years (range 4.3-7.5 years)
- **Mean time from the completion of primary course of vaccination**: 4.7 years (range 3-6.4 years)

Demographic and baseline characteristics between the two groups (those primed with Hexavac and those with Infanrix) were comparable.

**Pre-booster anti-HBs concentration in 1540 children primed with hexavalent vaccines 5 years previously**

- Hexavac: 119/709 (16.8%)
- Infanrix: 520/909 (57.2%)

**Pre-booster anti-HBs concentrations in children primed with Hexavac (n=831) and Infanrix (n=709)**

- Hexavac: 512/831 (61.6%)
- Infanrix: 319/831 (38.4%)

**Anti-HBs concentrations after booster with HB vaccine**

- Hexavac: 41/549 (7.5%)
- Infanrix: 6/105 (5.7%)

GMCs:
- Hexavac: 4.5 mIU/ml
- Infanrix: 61.3 mIU/ml

**p-value**
- p<0.05
- p=0.4
Side effects of a booster dose of monovalent HB vaccine

- Diary records were returned by 535/560 children.
- 55 children (10.3%) had transient mild reactions confined to the side of injection.
- No serious adverse events were reported.
- No difference between the two booster vaccine groups.

Anti-HBs response to an additional complete course of HB vaccination in 35/41 children with anti-HBs <10 mIU/ml after booster

<table>
<thead>
<tr>
<th>Vaccines primed with</th>
<th>N</th>
<th>&gt;100 mIU/ml</th>
<th>10 – 100 mIU/ml</th>
<th>GMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexavac</td>
<td>31</td>
<td>31 (100%)</td>
<td>-</td>
<td>584.5 mIU/ml</td>
</tr>
<tr>
<td>Infanrix</td>
<td>4</td>
<td>1 (25%)</td>
<td>3 (75%)</td>
<td>2756.8 mIU/ml</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>35</td>
<td>32 (91.4%)</td>
<td>3 (8.6%)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions - 1

- Five years after primary immunisation, the proportion of children with protective levels of anti-HBs is significantly lower in those vaccinated with Hexavac compared with those vaccinated with Infanrix Hexa.
- Responses to a booster dose of monovalent HB vaccine are consistent with the induction of immune memory against future HB infection regardless of pre-booster anti-HBs concentration.

Conclusions - 2

- No need for booster injections of vaccine to sustain immunity in children vaccinated in infancy with hexavalent vaccines.
- This observation is specific to the 5-year checkpoint. Additional follow-up is needed.