Impact of hepatitis B vaccine safety issues on vaccination strategies and their implementation in France

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VHPB - 19/11/2004
1982: Selective vaccination targeted to high risk groups

1992: Based on North-American experiences showing the inability of selective vaccination to control hepatitis B, World Health Assembly recommendation of “universal” vaccination in all countries

1994-1995: Adoption, in addition to the selective vaccination, of a 2-components vaccination strategy:

- Hep B vaccination included in infant vaccination schedule
- School-based vaccination campaigns for 11 year olds for a ten years period

- Infant vaccination: low coverage (≈30%)
- Pre-teenagers: high coverage (75 to 80%)
- High-risk populations: vaccination well beyond the target populations:
  - More than 75 millions doses sold by the end of 1997
  - More than 84% of these sales since 1994
  - More than 1/3 of the French population vaccinated
Hepatitis B vaccination in France
Coverage according to age - 1998

Source SOFRES medical/GSK
Vaccine safety data up to March 1998

Increasing number of notifications of adverse events following vaccination to the French Medicine Agency (AFSSAPS), mainly episodes of central demyelination (ECD)

Up to end of 03/98, 249 notifications of ECD (192 first episodes of central demyelination (FECD), 57 MS relapses)

Temporal association between a frequent exposure and a not so rare event in young adults (> 2000 MS/year in 20-49 years) ?

Number of FECD notified in the 2 months following vaccination in 20-44 years old, comparable with the expected number

Difficult to interpret in the context of an under-notification of AEs to the AFSSAPS and uncertainty about MS epidemiology
Case-control studies

Association between FECD and HB vaccination

- **Pilot study (Hôpital Pitié Salpetrière, 1997)**
  OR: 1.8 [0.5 - 6.0] for 2 months interval
  OR: 1.7 [0.8 - 3.7] all notifications

- **Multi-center study (France, 1998)**
  OR: 1.4 [0.4 - 4.5] 2 months, documented vaccination
  OR: 1.8 [0.7 - 4.6] 2 months, all subjects

- **GPRD data base study (UK, 1998)**
  OR: 1.4 [0.8 - 2.4] 2 months
  OR: 1.8 [0.6 - 3.9] 2 months

Neither confirm nor disprove a small increase in risk in adults
Number and attributable risk of FECD according to age, under the assumption of a causal relationship with vaccination 1990-1997. Source AFSSAPS/InVS

<table>
<thead>
<tr>
<th>Age at vaccination</th>
<th>Base-case scenario</th>
<th>Worst-case scenario</th>
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</thead>
<tbody>
<tr>
<td></td>
<td># of FEDC</td>
<td>Attributable risk per 10^5 vaccinees</td>
</tr>
<tr>
<td>0-1 years</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2-6 years</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7-9 years</td>
<td>5</td>
<td>0.23</td>
</tr>
<tr>
<td>10-12 years</td>
<td>7</td>
<td>0.08</td>
</tr>
<tr>
<td>13-15 years</td>
<td>9</td>
<td>0.19</td>
</tr>
<tr>
<td>16 years et plus</td>
<td>135</td>
<td>0.25</td>
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</tbody>
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Base-case scenario: OR = 1.4 / FEDC, 6/12 following vaccination, 100% exhaustiveness.

Worst-case scenario: OR = 1.8 / FEDC any time since vaccination, 50% exhaustiveness.
Estimated risk of FECD under the assumption of a causal association with HB vaccination and benefits of vaccination for a fictive cohort of 800,000 pre-teenagers followed-up to 35 years of age

<table>
<thead>
<tr>
<th></th>
<th>High incidence scenario</th>
<th>Low incidence scenario</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Best case scenario</td>
<td>Worst case scenario</td>
</tr>
<tr>
<td>Number of acute ulcerating hepatitis prevented</td>
<td>29</td>
<td>7</td>
</tr>
<tr>
<td>Number of cirrhosis prevented</td>
<td>147</td>
<td>29</td>
</tr>
<tr>
<td>Number of FECD attributable to vaccination</td>
<td>&lt; 2 FECD</td>
<td></td>
</tr>
</tbody>
</table>

Source: Bulletin épidémiologique hebdomadaire 9/99
Conclusions drawn by InVS - September 1998

**In infants**: no notification of neurological events following immunization

=> no reason to question the infant vaccination

**In adults**

- French data do not allow to discard a small excess risk
- Available international data in disfavor of an association
- If a neurological risk exists, it appears negligible for high risk individuals
  - risk of post-vaccine FEDC < 1/100,000 in adults vs. % of Ag HBs
  - 4 to 7 % in HIV subjects or STD consultants

**For pre-teenagers**

- Very few notifications of neurological events following immunization
- Crude risk/benefit analysis not in favor of discontinuation of vaccination
The Minister of Health Press Conference
1st October 1998

- Held in a very emotional context
Hépatite B : les risques de la vaccination

Une affaire de l’ampleur de celle du sang contaminé risque-t-elle d’éclater bientôt ? La vaccination contre l’hépatite B entraîne des effets secondaires souvent redoutables, dont les cas se multiplient. Or, les patients n’en sont pas avisés…
Held in a very emotional context

Continuation of the 3 vaccination strategies

Discontinuation of the school-based campaigns

Immunization of pre-adolescents possible as individual vaccinations in private practice

Change for pre-adolescents justified by the need to “better take into account the individual benefits and risks”
Impact of the decision

The discontinuation of school-based campaigns was, up to a certain extend, interpreted as a recognition of a safety issue and created some confusion in media, public and medical community.

Continuation of the decrease in vaccination activities as shown by vaccine sales data.
Number of prescribed VHB vaccine doses in the private sector - Infant and pre-adolescent vaccinations, 1990-99
Impact of the decision

- The discontinuation of school-based campaigns was, up to a certain extend, interpreted as a recognition of a safety issue and created some confusion in media, public and medical community.

- Continuation of the decrease in vaccination activities as shown by vaccine sales data.

- Current low coverage in infants and pre-adolescents:
  - Coverage at 24 months in 2003: 28%.
  - School health surveys (MoH, Ministry of Education, InVS):
    - 2000-01: 67% in 14–16 years old.
    - 2001-02: 30% in 10–11 years old.
Hepatitis B vaccination coverage in France according to age - 2002

Source: SOFRES medical/GSK
Impact of the decision

The discontinuation of school-based campaigns was, up to a certain extend, interpreted as a recognition of a safety issue and created some confusion in media, public and medical community.

Continuation of the decrease in vaccination activities as shown by vaccine sales data.

Current low coverage in infants and pre-adolescents.

Available data in favor of decreasing coverage in high risk populations (except health staff): new patients in an IVDU clinic: 45% and 22% coverage resp. in 1999 and 2001.
Position of the various public stakeholders

Expert committees

- Advisory board in immunisation (CTV) has regularly reviewed the data and invariably advised the MOH to maintain the 3-tiered vaccination strategy.

- Last statement dated mid-September 2004: “no indication to modify the current recommendations”

- Special ad hoc expert committee set up by the MOH has come up with the same conclusions (Commission Dartigues, 2001)

- Same conclusions reiterated by the jury of the “consensus conference” including some of the best expertise available globally on the topic (September 2003)

- Continuous commitment in favor of vaccination of professional Societies of Hepatology
Position of the various public stakeholders
Ministry of Health

“Available data do not allow to rule out the hypothesis of a weak association…

However, there is no reason to question the current immunisation strategies”

Actually, no change in the immunisation schedule since 1995 (other than discontinuation of the 4 doses schedule and of the booster doses, narrowing of high risk groups definition in 1998)

The 2004 immunization schedule still recommends:

- Vaccination of children before 13 years of age
- Best done in infancy
- Catch-up for pre-teenagers at 11-13 years
- Vaccination at any age of high risk subjects
- Mandatory vaccination of health professionals