Follow-up of hepatitis B vaccination in Canada

Bernard Duval, md, mph, fr CPC
Institut National de Santé Publique du Québec
Québec, Canada
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HB in Canada

- Low endemicity:
  - HBsAg+: 0.5%
  - Serological VHB markers: 5%
- Peak incidence: 15-40 y-o
- Three licensed vaccines:
  - Recombivax-HB
  - Engerix-B
  - Twinrix
Provincial/Territorial HB Vaccination Practices in Canada

- Infants vaccination
- 8-13-year-old children vaccination
Provincial/Territorial HB Vaccination with paediatric or adult doses in children

- **Pediatric dosage**
  - BC
  - AB
  - SK
  - MB
  - ON
  - QC
  - NF
  - PEI
  - NS
  - NB

- **Adult dosage**
  - YK
  - NWT
  - NU
## Routine Immunization Schedule for HB Vaccination

<table>
<thead>
<tr>
<th>Province/Territory</th>
<th>Infant HB vacc.</th>
<th>School HB vacc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberta</td>
<td>Selective</td>
<td>Gr 5</td>
</tr>
<tr>
<td>British Columbia</td>
<td>2, 4, 6 mo</td>
<td>Gr 6</td>
</tr>
<tr>
<td>Manitoba</td>
<td>Selective</td>
<td>Gr 4</td>
</tr>
<tr>
<td>New Brunswick</td>
<td>0, 2, 12 mo</td>
<td>Gr 4</td>
</tr>
<tr>
<td>Newfoundland</td>
<td>Selective</td>
<td>Gr 4</td>
</tr>
<tr>
<td>Northwest Territories</td>
<td>0, 1, 6 mo</td>
<td>Gr 4</td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>Selective</td>
<td>Gr 4</td>
</tr>
<tr>
<td>Nunavut</td>
<td>0, 1, 9 mo</td>
<td>Gr 4</td>
</tr>
<tr>
<td>Ontario</td>
<td>Selective</td>
<td>Gr 7 (0,6)</td>
</tr>
<tr>
<td>Prince Edward Island</td>
<td>2, 4, 15 mo</td>
<td>Gr 3</td>
</tr>
<tr>
<td>Quebec</td>
<td>Selective</td>
<td>Gr 4</td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>Selective</td>
<td>Gr 6</td>
</tr>
<tr>
<td>Yukon</td>
<td>2, 4, 12 mo</td>
<td></td>
</tr>
</tbody>
</table>
Routine Immunization in Quebec

• Given in school since 1994
• Grade 4 pre-teenagers (9 year-old)
• Vaccines (tenders):
  – Recombivax-HB 2,5µg (since 1996)
  – Engerix-B 10µg (1994-6)
• Schedule: 3 doses (0, 1, 6)
• Free of charge, written parental consent
• Coverage: 90%
• Catch-up: 2 yearly cohorts, selective
HB incidence rates (notifications) by age, Quebec, 1990-2002
HB incidence rates by 2-year period and age group

incidence rate/100,000

0-4 5-14, 15-19 20-24 25-29 30-34 35-39 40-49 50-59 60+

Quebec Long-term HB study

• 15 year cohort study started in 1996
• Goals:
  - To measure the proportion of children who would still be protected at age 25
  - Need for a booster dose
  - If needed, age for booster
General study objectives

• Primary
  - To evaluate the persistence of antibodies to EB and RB in all subjects at age 25 and compare the levels obtained in those given a booster injection at age 15 or age 20 with those receiving no booster injection.
  - Secondary
    - To determine the antibody levels at age 15 and age 20, 5 and 10 years after primary vaccination.
    - To determine the effect on antibody levels of a booster injection at age 15, 20 and 25 years.
    - To evaluate the reactogenicity of the booster dose.
General study design

• Baseline antibody measurement
• Randomisation of the cohort in 3 groups
• For each group, after respectively 5, 10 or 15 years:
  – Blood sample pre-booster
  – Booster dose
  – Blood sample one month and one year after booster
General study Method (1)

• Year 0: 2255 subjects vaccinated in 1995-97
• Year 0 Vaccines: Engerix-B 10µg or Recombivax-HB 2.5 µg (0,1,6)
• Year 5: 1962 remaining subjects were randomized in 3 groups (A,B,C)
• Booster vaccines: appropriate for age
  – Year 5: Engerix-B 10µg, Recombivax-HB 5µg
• Yearly contacts: newsletter,…
General study method (2)

• For all groups:
  – Anti-HBs, anti-HBc, HBsAg after primary vaccination and before booster dose
  – Anti-HBs, anti-HBc, HBsAg at year 15 of the study
  – Anti-HBs one month and one year after the booster dose
Study design for booster vaccination at 5, 10 and 15 years

Group A: 5-year Booster
- Vaccin.: BS, PBS, PBS, PBS
- Year: 5, 5+30 days, 6, 10, 10+30 days, 11
- Visit: 1, 2, 3, 4, 5, 6, 7, 8

Group B: 10-year Booster
- Vaccin.: BS, PBS, PBS, PBS
- Year: 10, 10+30 days
- Visit: 5, 6
- Group: A&B

Group C: 15-year Booster
- Vaccin.: BS, PBS
- Year: 15, 15+30 days
- Visit: 7, 8
- Group: C
Proportion of subjects with anti-HBs ≥ 10 mIU/ml
Log anti-HBs GMTs

month 1          year 5          year 6

10000000
1000000
100000
10000
1000
100
10
1

Engerix   Recombivax
# Anti-HBs titers after the primary vaccination and after the booster

<table>
<thead>
<tr>
<th>Anti-HBs level one month after primary vaccination (mIU/ml)</th>
<th>N</th>
<th>0</th>
<th>1-9 (mIU/ml)</th>
<th>10-99</th>
<th>100-999</th>
<th>1000-9999</th>
<th>≥ 10 000</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-99</td>
<td>11</td>
<td>2 (18.2)</td>
<td>3 (27.3)</td>
<td>3 (27.3)</td>
<td>1 (9.1)</td>
<td>2 (18.2)</td>
<td></td>
</tr>
<tr>
<td>100-999</td>
<td>78</td>
<td></td>
<td></td>
<td>4 (5.1)</td>
<td>25 (32.0)</td>
<td>38 (48.7)</td>
<td>11 (14.1)</td>
</tr>
<tr>
<td>1000-9999</td>
<td>282</td>
<td></td>
<td></td>
<td>8 (2.8)</td>
<td>78 (27.7)</td>
<td></td>
<td>196 (69.5)</td>
</tr>
<tr>
<td>≥ 10 000</td>
<td>202</td>
<td></td>
<td></td>
<td></td>
<td>5 (2.5)</td>
<td></td>
<td>197 (97.5)</td>
</tr>
<tr>
<td>Total</td>
<td>573</td>
<td>2 (0.35)</td>
<td>3 (0.5)</td>
<td>7 (1.2)</td>
<td>34 (5.9)</td>
<td>123 (21.5)</td>
<td>404 (70.5)</td>
</tr>
</tbody>
</table>
### Anti-HBs titers one month and one year after the booster

<table>
<thead>
<tr>
<th>Anti-HBs level one month after the booster dose (mIU/ml)</th>
<th>N</th>
<th>Anti-HBs level one year after the booster dose (mIU/ml), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>1 (50)</td>
</tr>
<tr>
<td>1-9</td>
<td>2</td>
<td>1 (50)</td>
</tr>
<tr>
<td>10-99</td>
<td>7</td>
<td>3 (42.9)</td>
</tr>
<tr>
<td>100-999</td>
<td>34</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>1000-9999</td>
<td>120</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>≥ 10 000</td>
<td>395</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>560</td>
<td>2 (0.35)</td>
</tr>
</tbody>
</table>
Summary 1
Persistence of antibodies

• 5 years after primary immunization:
  - 5.1% had no detectable anti-HBs
  - 15.4% had a titer inferior to the seroprotective level
  - no subject became anti-HBc+
  - no subject had an increased anti-HBs titer
Summary 3
Persistence of protection

- **One year after the booster dose:**
  - 2 subjects (0.36%) had no detectable anti-HBs titers
  - 9 subjects (1.6%) had a titer between 1-9 mIU/ml

- These 11 subjects:
  - All had a titer between 10 and 99 mIU/ml after primary vaccination
  - All had a titer between 0 and 9 before the booster
Geometric mean titer

• GMTs were higher in the EB than in the RB group (p<0.001) at each point

• 5 years after primary vaccination: 29-fold decrease of GMT in EB and 56-fold in RB group

• One month after the booster: 449-fold rise in EB and 252-fold rise in RB group

• Strong correlations between initial, 5 years pre-booster, 1 month and 1 year post-booster dose anti-HBs titers (r=0.72-0.95; p<0.0001)
Discussion (1)

• 1% of all subjects over 10 mIU/ml after primary immunization remained under this titer after the 5-year booster, which may suggest that they had no remaining immune memory.

• 5 out of 11 (45%) subjects with anti-HBs 10-99 mIU/ml after primary vaccination remained under 10 mIU/ml after the 5-year booster. It may suggest that this titer is not an adequate predictor of long-term protection in this population.
Conclusions

- EB 10 µg and RB 2.5µg are highly immunogenic in 9-10-year olds and provide a protection for at least 5 years in 99% vaccinees with a titer ≥ 10 mIU/ml after primary vaccination.

- A titer of<100mIU/ml of anti-HBs after primary vaccination in pre-teenagers may not be enough for long term protection

- A booster dose is not required after 5 years but a longer follow-up is necessary for taking a decision about the booster dose in pre-teenagers vaccinated with paediatric doses of vaccine

- It will be important to see what will be the proportion of the seroprotected young adults and the proportion of responders to a challenge with a booster dose given 10 and 15 years after the vaccination
Acknowledgements

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Some unpublished data is not disclosed in this online version