Long-term immunity induced by hepatitis A vaccines: an update

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Outline of the talk

• Observed anti-HAV antibody persistence
  - in adults
  - in children
• Model-based predictions
  - (log)linear extrapolation
  - linear mixed model
• From antibody persistence to persistence of protection
• Unsolved issues
Antibody persistence

- Anti-HAV persistence ≥ cut-off level
  - Different cut-off levels (10, 15, 20, 33 IU/L)
- Many years after completion of vaccination schedule
  - very few subjects lose their antibodies
    - children: up to 11 years
    - adults: up to 15 years, and still ongoing (Y16-Y20)
  - also in unselected populations (Rendi-Wagner et al.)
    - >1000 fully vaccinated travellers
    - blood sample ±10 years later
    - 98% still had anti-HAV >10 IU/L

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AB persistence: hepatitis A
Linear extrapolation (1994-2001)

Model-based predictions

- Log-linear extrapolation method (average persistence)
  - children: 14-25 years
  - adults: 20-25 years (and beyond)
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Estimation Period

STEP 1:
Modeling the change in antibody level in the estimation period
Results

- **Input data**
  - antibody level before second vaccine dose
  - body mass index (BMI)

- **Model fits the data well**
  - at population level
  - at individual level
Long-Term Predictions

STEP 2:
Long term prediction
First Step: Validation of the model

- **Validation of the model**

**ESTIMATION PERIOD**

**PREDICTION PERIOD**

Prediction based on the first 6 years

New observation (e.g., year 7)

Correlation between the predicted value at 7 years (based on 6 years data) and the observed value.
HAV123 (0-6): correlation

$\mathbf{r = 0.96}$
HAV112 (0-12): correlation

All but 3 seronegative subjects: $r = 0.97$

All subjects: $r = 0.81$
Results

• Input data
  • antibody level before second vaccine dose
  • body mass index (BMI)

• Model fits the data well
  • at population level
  • at individual level

• High correlation with observations
  • at population level
  • at individual level
2004: Model validation

- Using data up to year 6 (like in 2000)
  - Different models
    - Model 2000 (fractional polynomial with covariates)
    - Model 2000 without covariates
    - Linear trend with changepoint (like Bovier et al.)
  - Predicting data year 7-10
    - Results:
      - excellent correlation (~0.90)
      - slightly ↓ with time
Mean Structure (1): linear model with a change point

For $t_j < T$:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i}) t_j + \varepsilon_{ij}$$

For $t_j \geq T$:

$$Y_{ij} = (\beta_0 + \alpha_0 + b_{0i}) + (\beta_1 + \alpha_1 + b_{1i}) t_j + \varepsilon_{ij}$$

- We allow for a change in linear trend.

Evolution of the mean

![Graph showing the evolution of the mean with a change point at T](image)
Second Step: Long-Term Predictions

HAV-123

estimation period prediction period

Linear Model
Loess (est. period)

MONTH 120
MONTH 360
Hepatitis A: Linear mixed model
Long-term estimates

- Individual predictions after 25 years (2000)
  - anti-HAV before 2nd dose % neg. at Y25
  - < 20 IU/L < 12 %
  - 20-100 IU/L < 8 %
  - 100-1000 IU/L < 2 %
  - > 1000 IU/L < 1 %
  - overall < 5 %

- Confirmed in 2004 (including Y6-Y10 data)
  - consistent results with 3 different models

- Similar results with other vaccines

Bovier 2002; Bovier (CISTM) 2005; Pigeon 1999; Van Herck (ISVHLD) 2000, 2004
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Long-lasting protection

• Minimal protective level?
  - not clearly defined
    • Studies in chimpanzees with passive immunisation
      - 10 IU/L: prevent viral shedding (but not infection)
    • Vaccine trials: different (in-house) ELISA tests
      - 10, 15, 20, 33 IU/L?
      - comparability of results?
  - Defining “protection”
    - Merriam-Webster: “the state of being protected”
      » 1 a : to cover or shield from exposure, injury, damage, or destruction
    - Shielded from exposure?
    - Shielded from “injury”?

Purcell, Vaccine 1992
Long-lasting protection

- Beyond persistence of antibodies
  - Direct evidence
    - Chimpanzees
      - Challenged with HAV after vaccination
        » Protected, even without anti-HAV antibodies
        » Antibodies are not an absolute requirement for protective immunity
    - Humans
      - In vitro tests for cellular-mediated immunity (EliSpot)
        » memory B-cells producing IgG anti-HAV 2-3 years post-vaccination
        » T-cell immune memory: up to 6 years post-vaccination

Chen 1996; Lemon 1993; Leroux-Roels 2000; Purcell 1992
Indirect evidence: booster study

- 12 years since Havrix 720 (0-1-6)
- Cohort (N=150) followed for 10 years
- Booster study: n=31
- Booster: Havrix 720
- Anamnestic response
  - titre at least x2 (or x4 if <100 IU/L at day 0)
- Day 0: 100% seropositive
- Fast, strong response within 2 weeks

Van Herck 2004
follow-up Month 145

- GMT 242 IU/L
- GMT 877 IU/L
- GMT 3831 IU/L
- GMT 5282 IU/L
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Unsolved issues (1)

• Observed anti-HAV persistence >15 years
  • follow-up Y16-Y20 started 11/2008

• Validation of model-based predictions
  • using Y11-Y15 follow-up data
  • like before OR restart model fitting from scratch?

• Mathematical modelling (Fraser 2007 – HPV)
  - modified power-law model
    • estimating the proportion of memory cells induced
    • applicable to other vaccines / infectious diseases?
    • similar fit as statistical modelling?
Unsolved issues (2)

• Extrapolation to other populations
  • other hepatitis A vaccines
  • vaccinated children and adolescents
  • vaccinated infants (effect of MATABs?)

• Duration of protection
  • boostability in absence of anti-HAV
    - pre-booster cellular-mediated immunity
    - immune response to booster dose
      » humoral
      » cellular
  • after single dose
After single dose: how long protected?

- Insufficient data, BUT good indications
  - Delayed second dose (up to 5-8 years)
    - Excellent anamnestic response to second dose
      - Not affected by the delay
      - Even after losing detectable antibodies
  - Single dose of live vaccine
    - Long-term persistence of antibodies and long-term effectiveness

- CAVE:
  - on the long run?
  - if vaccinated at young age?
  - in conditions of low endemicity?
  - no natural boosters

# Hepatitis A

## Delayed second dose

<table>
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<tr>
<th>Number (n)</th>
<th>Time of delay (month)</th>
<th>GMT before (IU/L)</th>
<th>GMT after (IU/L)</th>
<th>Ref.</th>
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<td>66</td>
<td>1544</td>
<td>Williams 2003</td>
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<td>18-54*</td>
<td>39-50</td>
<td>2385</td>
<td>Beck 2003</td>
</tr>
</tbody>
</table>

*°JTM 2004: up to 8 years
*CISTM_2007 poster: 8-11 years