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

Koen Van Herck, MD, PhD
Centre for the Evaluation of Vaccination
Vaccine & Infectious Disease Institute
University of Antwerp, Belgium

- 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

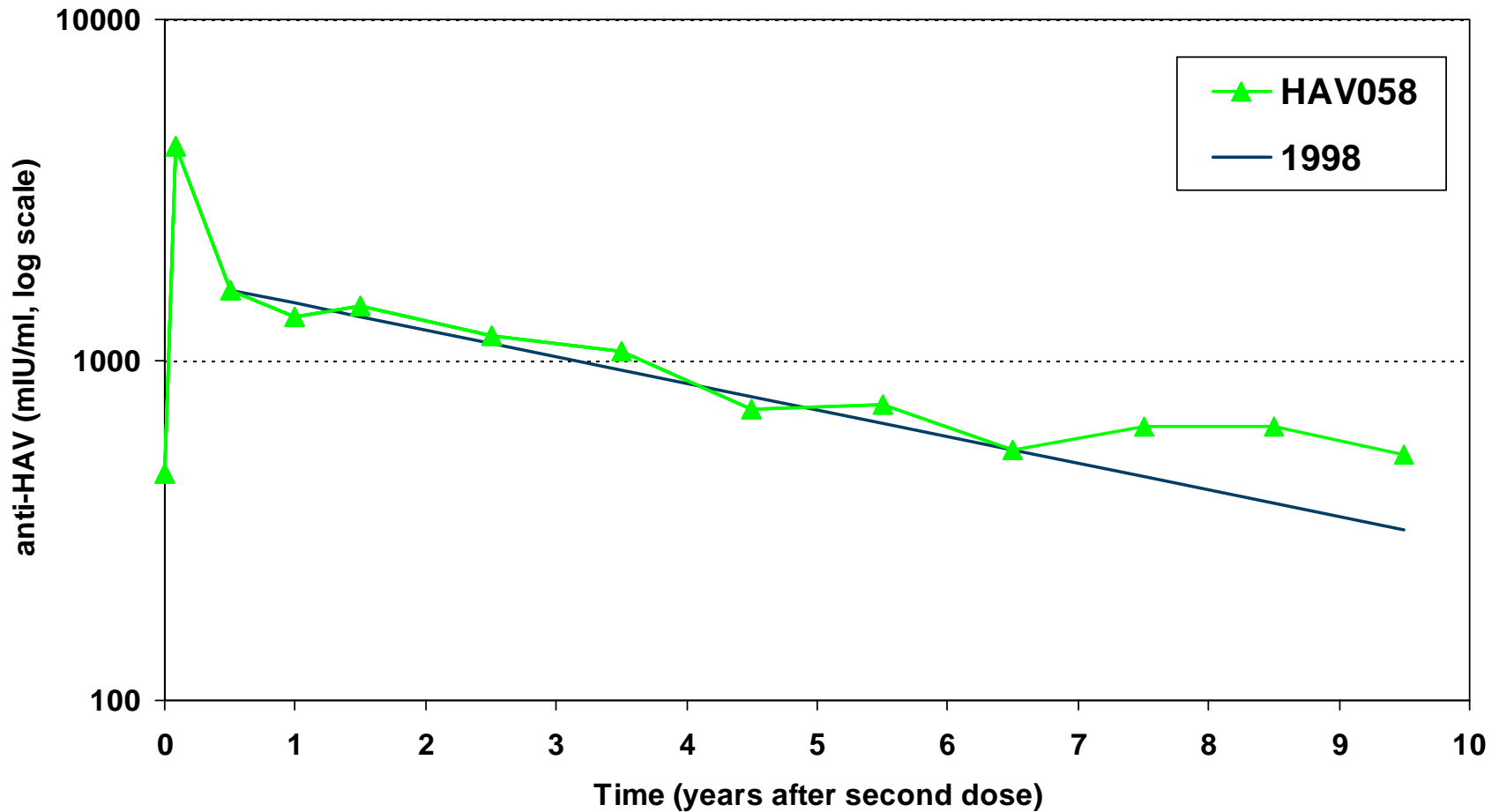
- Anti-HAV persistence \geq cut-off level
 - Different cut-off levels (10, 15, 20, 33 IU/L)
- Many years after completion of vaccination schedule
 - very few subjects lose their antibodies
 - children: up to 11 years
 - adults: up to 15 years, and still ongoing (Y16-Y20)
 - also in unselected populations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

Bovier 2002; Bovier (CISTM) 2005; Chan 1999; Dagan 2005; Diaz-Mitoma 2008; Fan 1998; Hammitt 2008; Maiwald 1997; Mayorga (ICAAC) 2003; Rendi-Wagner 2006; Totos 1997; Van Herck 2000; Van Herck 2001; Wang 2007; Wiedermann 1997; Wiedermann 1998; Wiens 1996

Outline of the talk

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



Van Damme et al, J Med Virol 1994

Model-based predictions

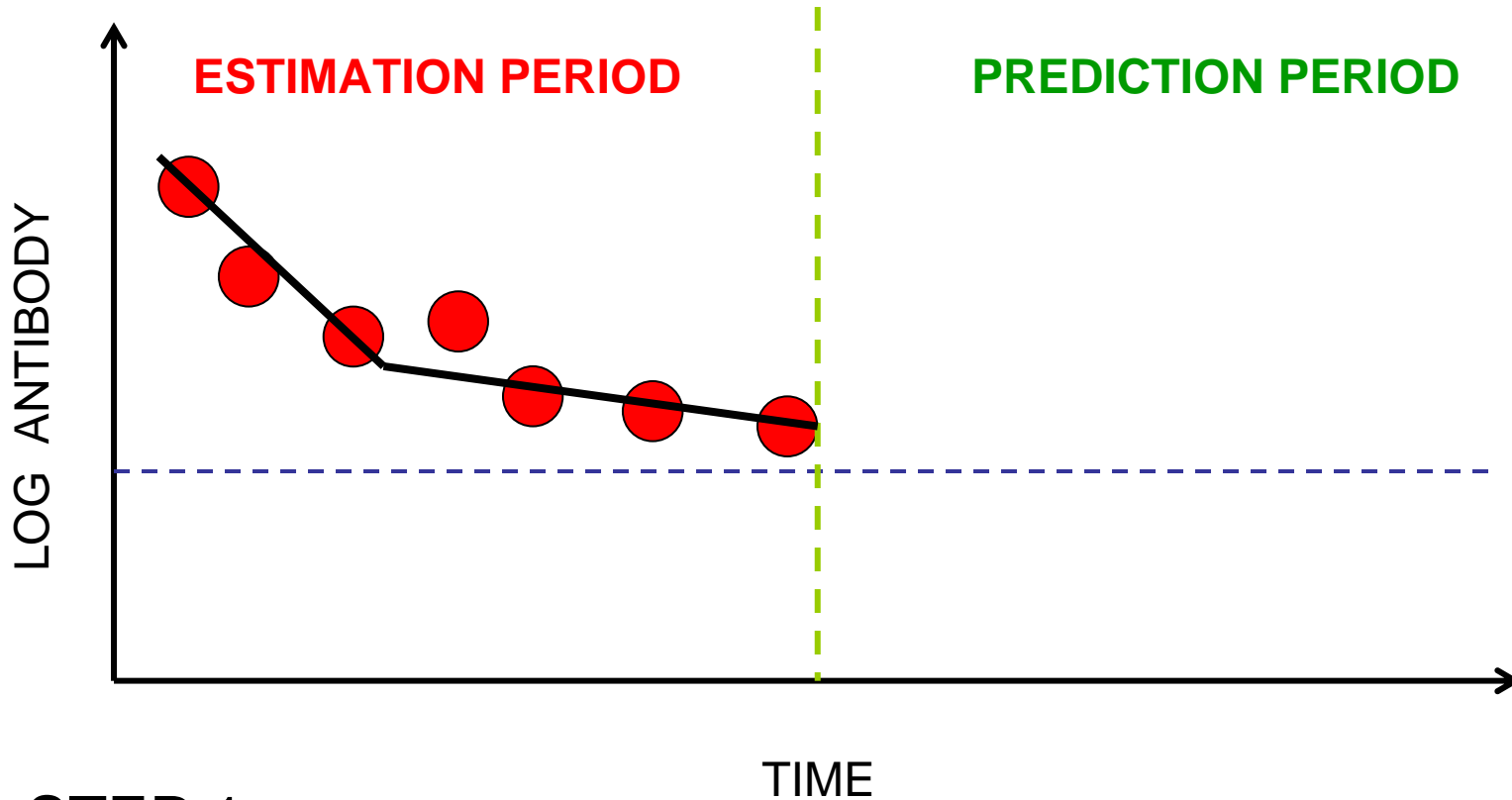
- Log-linear extrapolation method (average persistence)
 - children: 14-25 years
 - adults: 20-25 years (and beyond)

Bovier 2002; Fan 1998; Chan 1999; Maiwald 1997; Mayorga (ICAAC) 2003;
Rendi-Wagner, Vaccine 2006; Totos 1997; Van Herck 2000; Van Herck 2001; Wang 2007
Wiedermann 1997; Wiedermann 1998; Wiens 1996

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Estimation Period

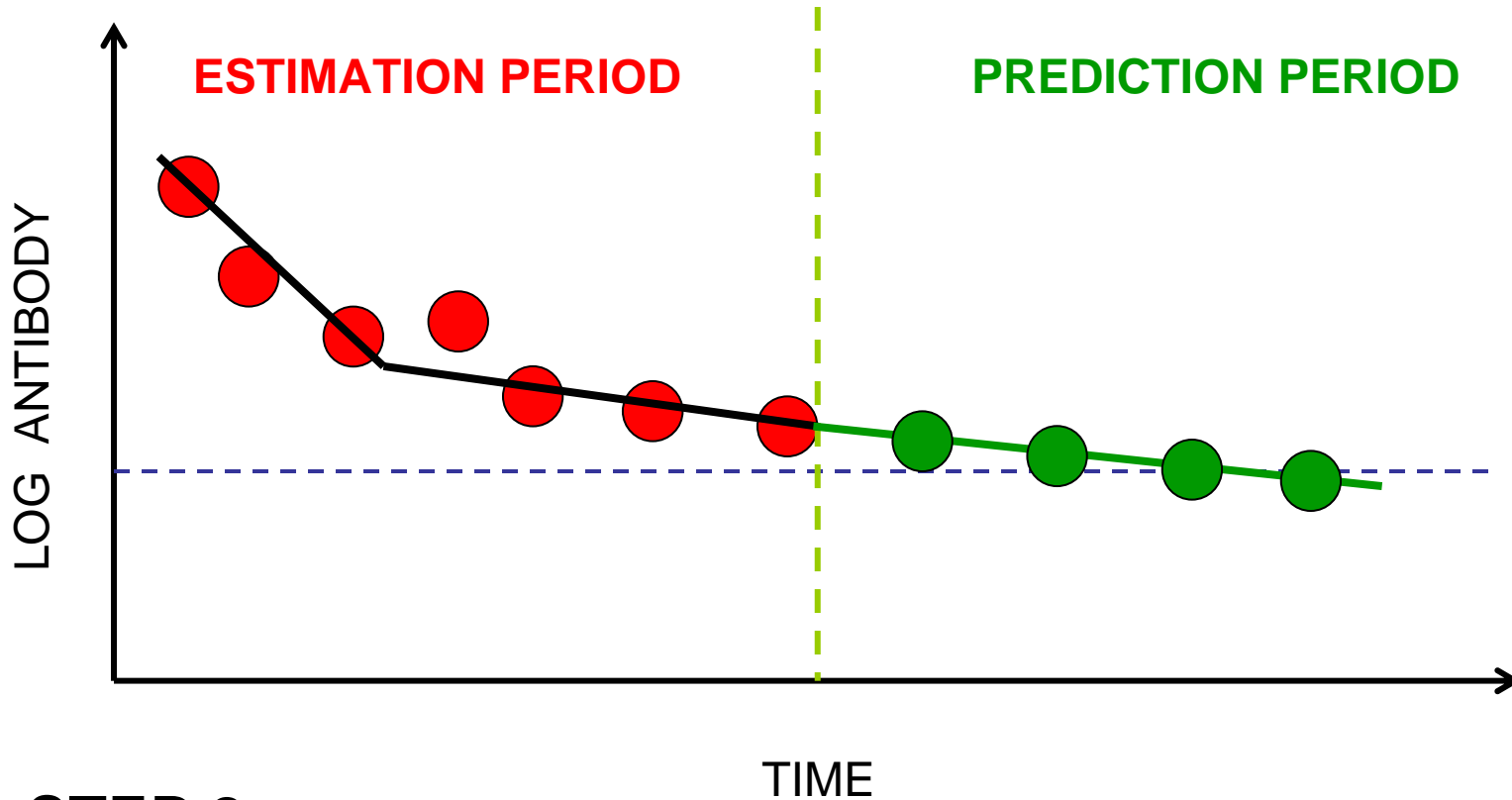


STEP 1:

Modeling the change in antibody level in the estimation period

- Input data
 - antibody level before second vaccine dose
 - body mass index (BMI)
- Model fits the data well
 - at population level
 - at individual level

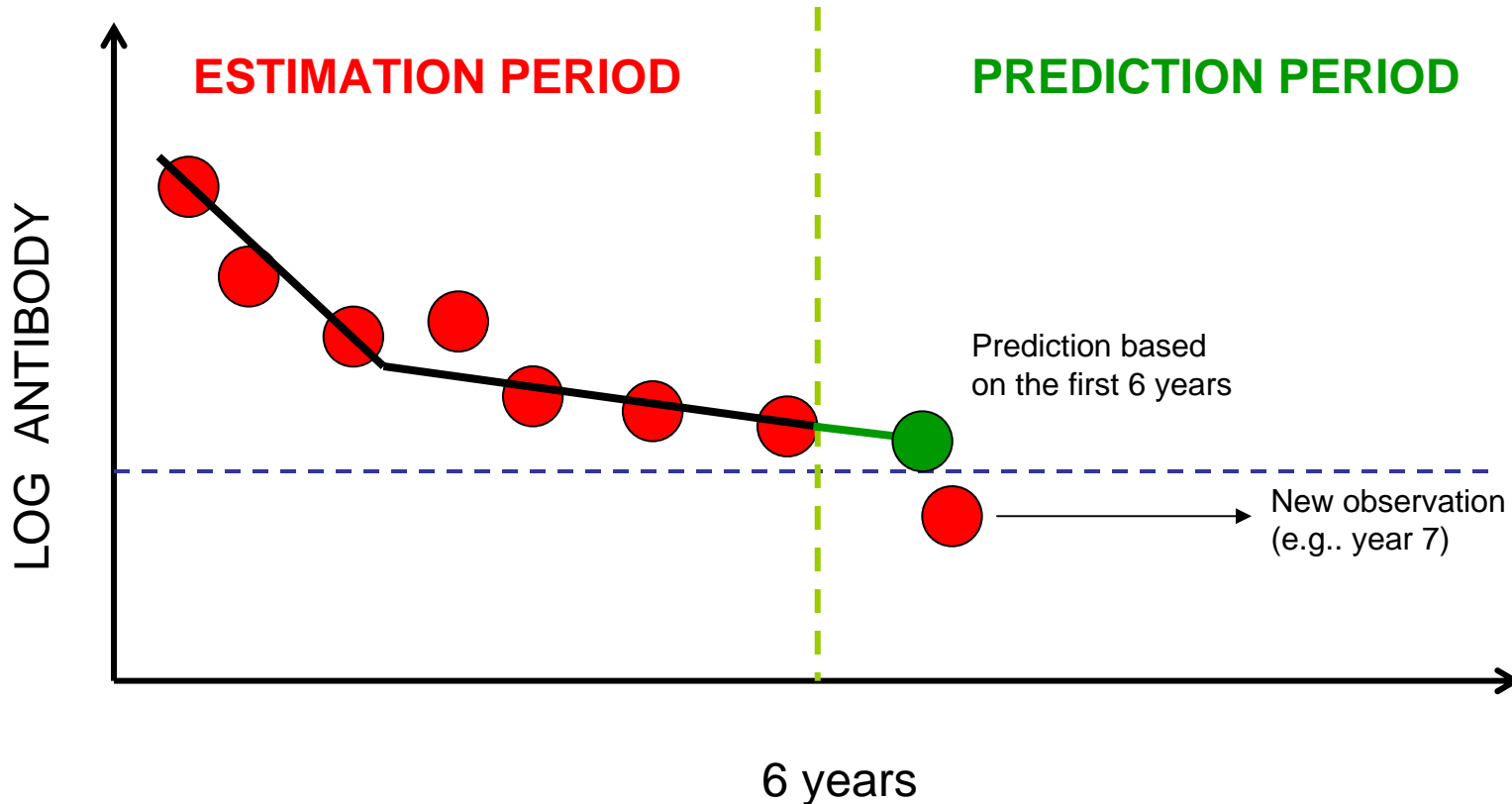
Long-Term Predictions



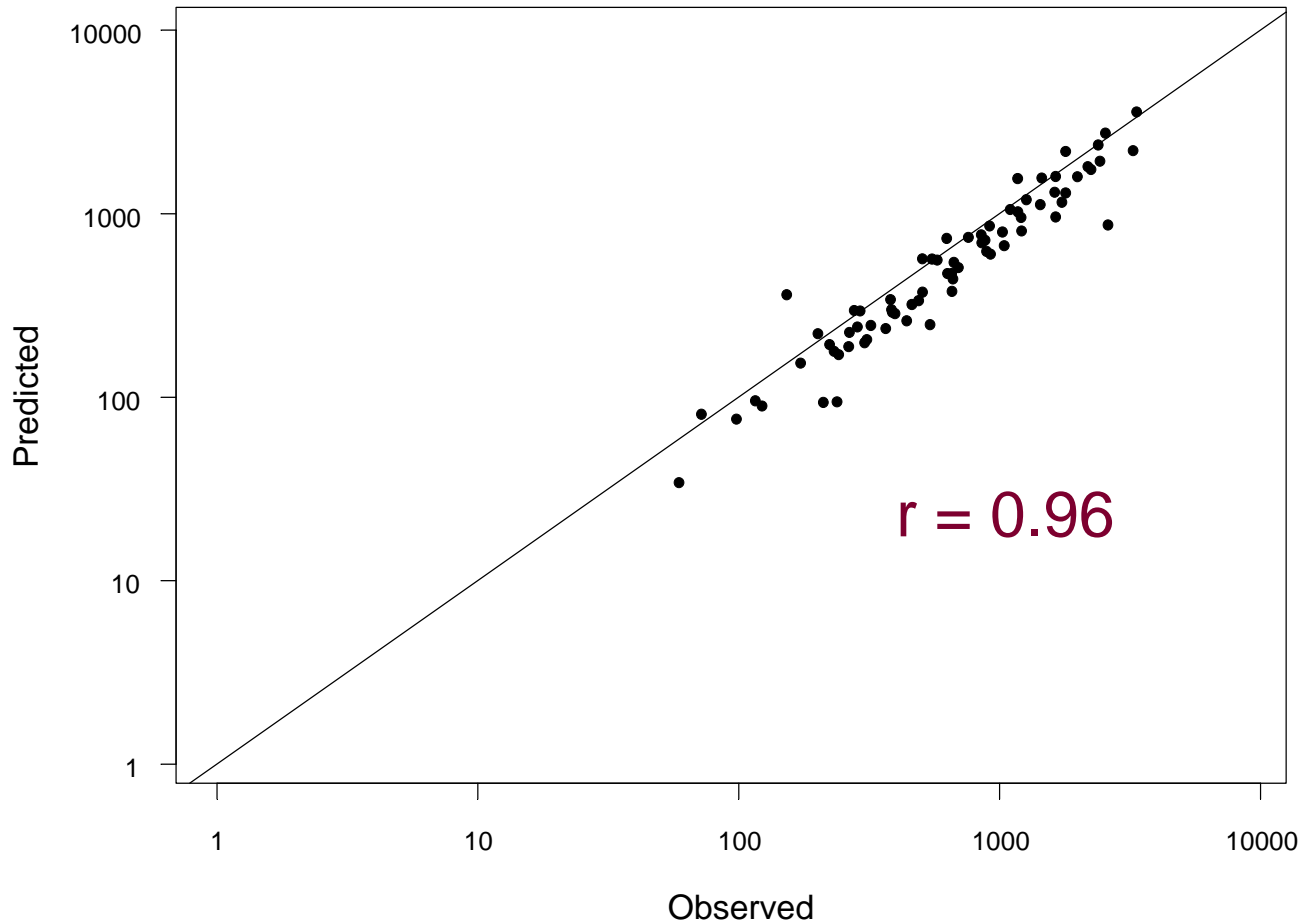
STEP 2:

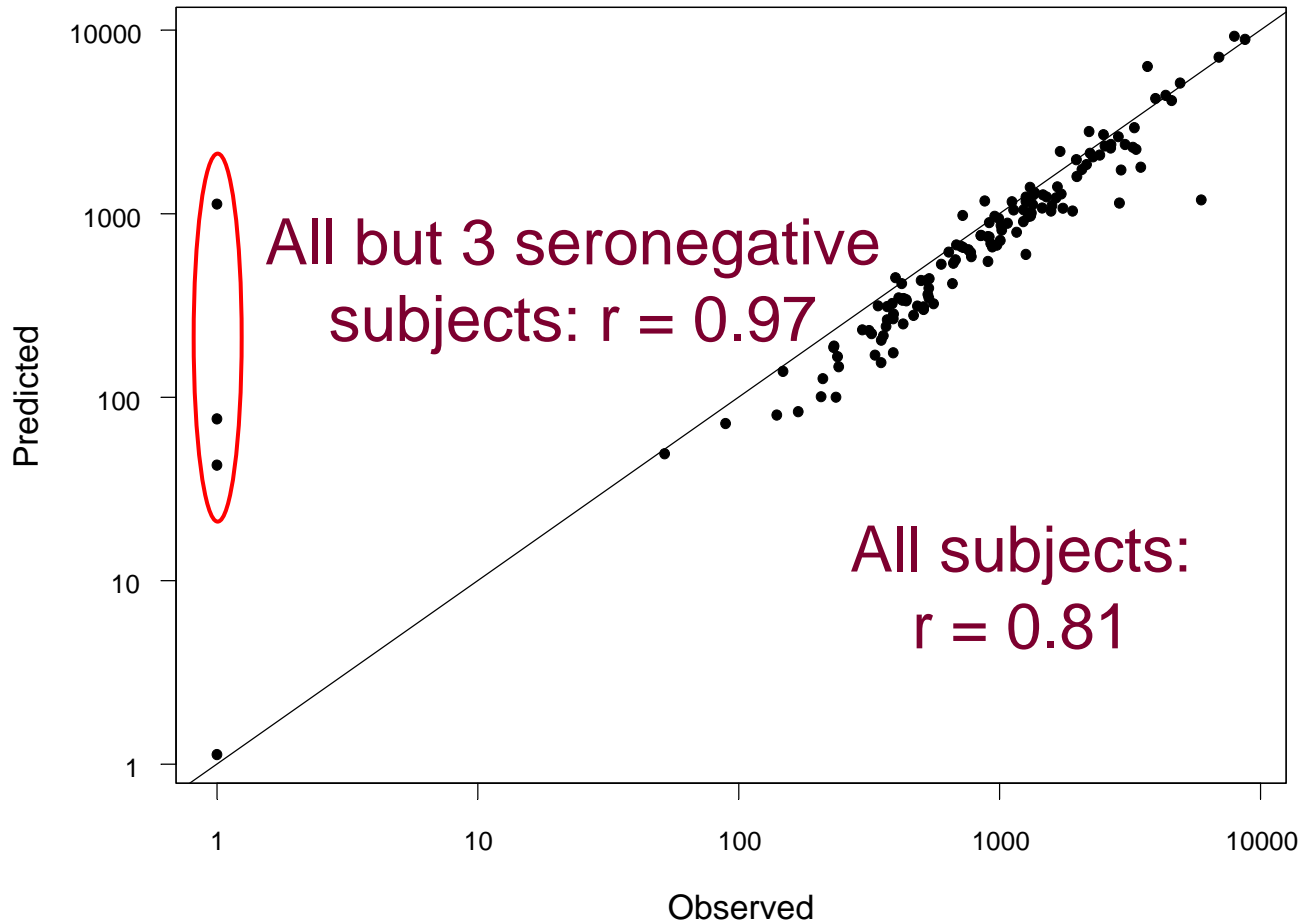
Long term prediction

First Step: Validation of the model



Correlation between the predicted value at 7 years (based on 6 years data) and the observed value.





- 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

- 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 \downarrow with time

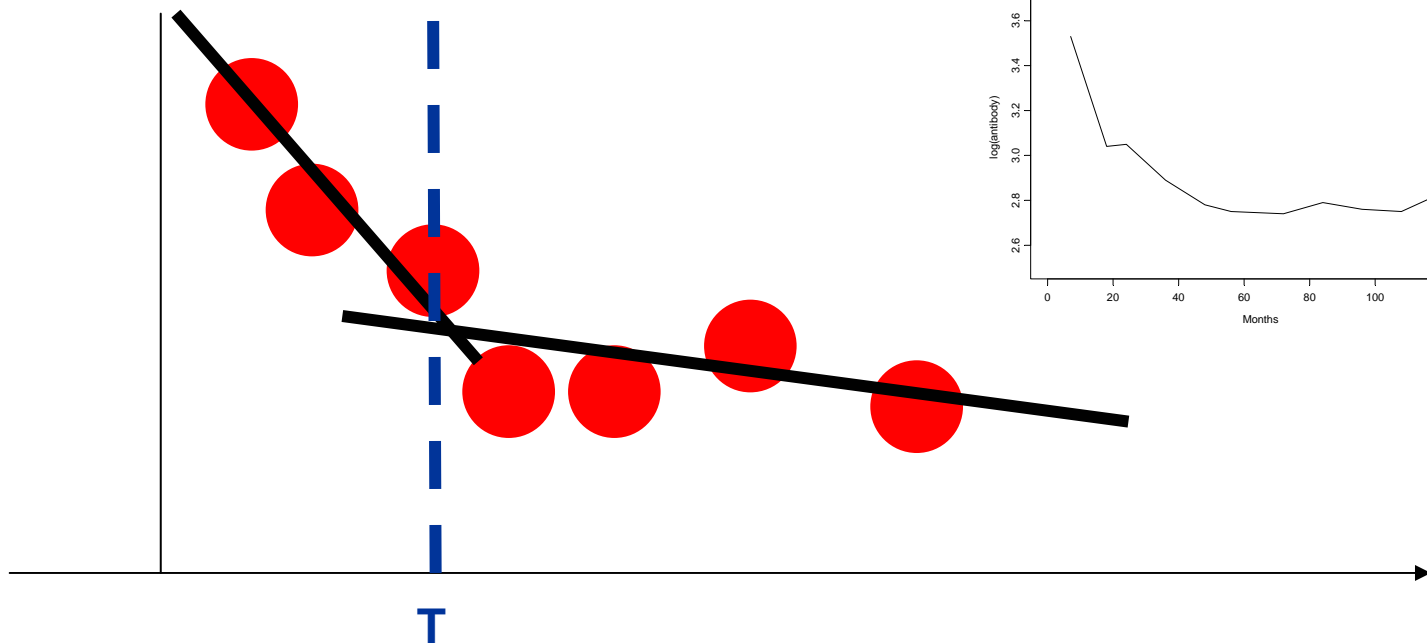
Mean Structure (1): linear model with a change point

For $t_j < T$:

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

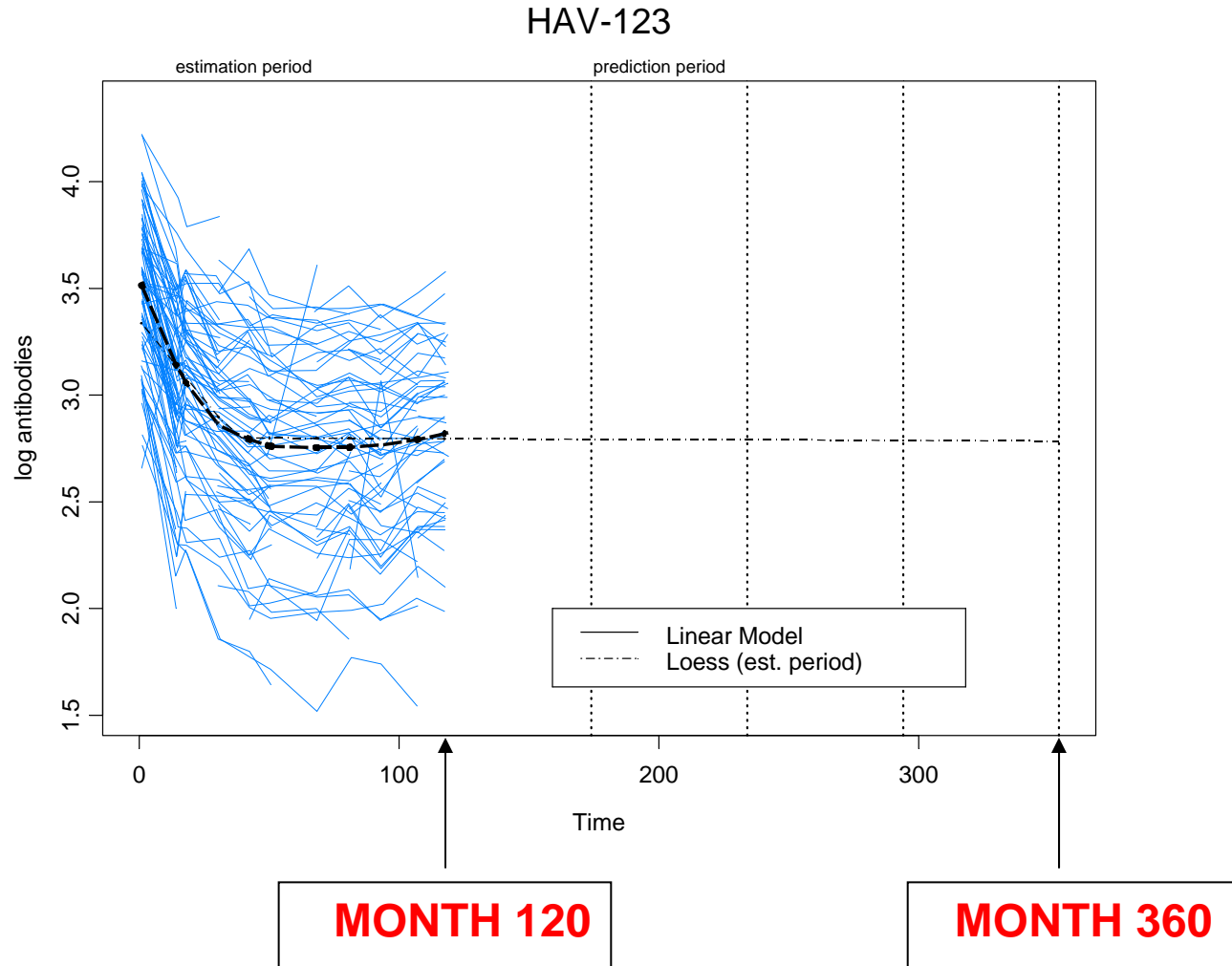
For $t_j \geq T$:

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



- We allow for a change in linear trend.

Second Step: Long-Term Predictions



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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- 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”?

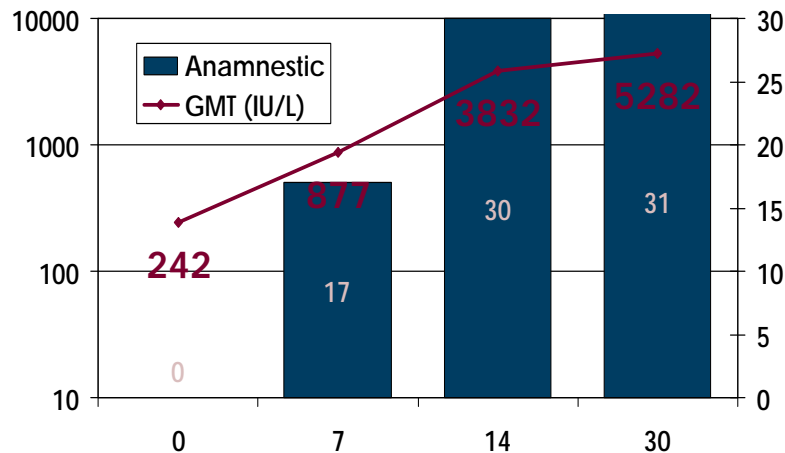
Purcell, Vaccine 1992

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

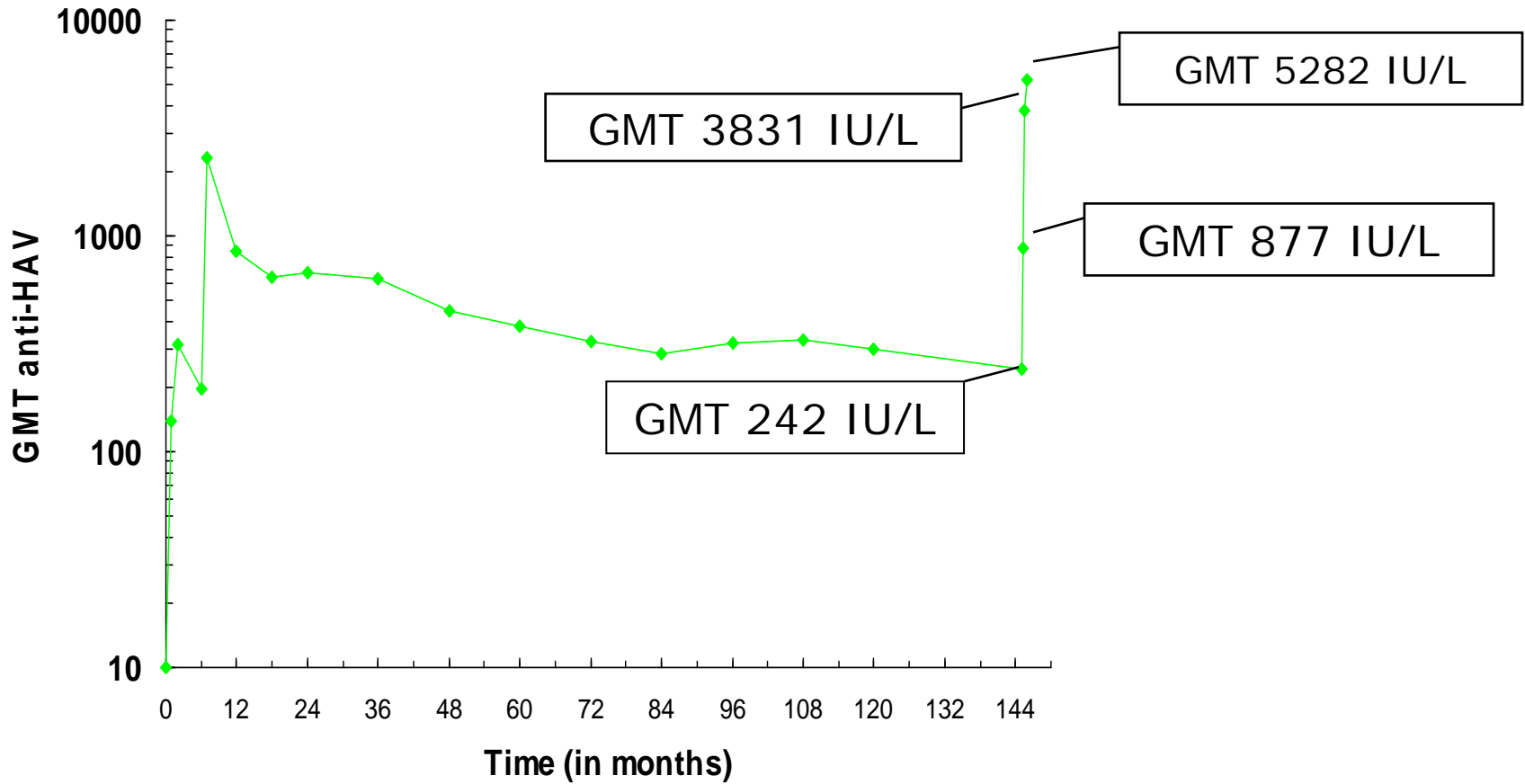
Indirect evidence: booster study



- 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



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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?

- 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

Beck 2003; Iwarson 2002; Iwarson 2004; Landry 2000; Orr 2006;
Wang 2007; Williams 2003; Zhuang 2005

Hepatitis A

Delayed second dose

Number (n)	Time of delay (month)	GMT before (IU/L)	GMT after (IU/L)	Ref.
124	24–66	116	3342	Landry 2000
25	48–72 [°]	32	2993	Iwarson 2002
156	20-31	66	1544	Williams 2003
97	18-54*	39-50	2385	Beck 2003

[°]JTM 2004: up to 8 years

*CISTM_2007 poster: 8-11 years