Vaccine & Infectious Disease Institute

Centre for the Evaluation of Vaccination

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Long-term immunity induced y hepatitis A vaccines: an upda e

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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

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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

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

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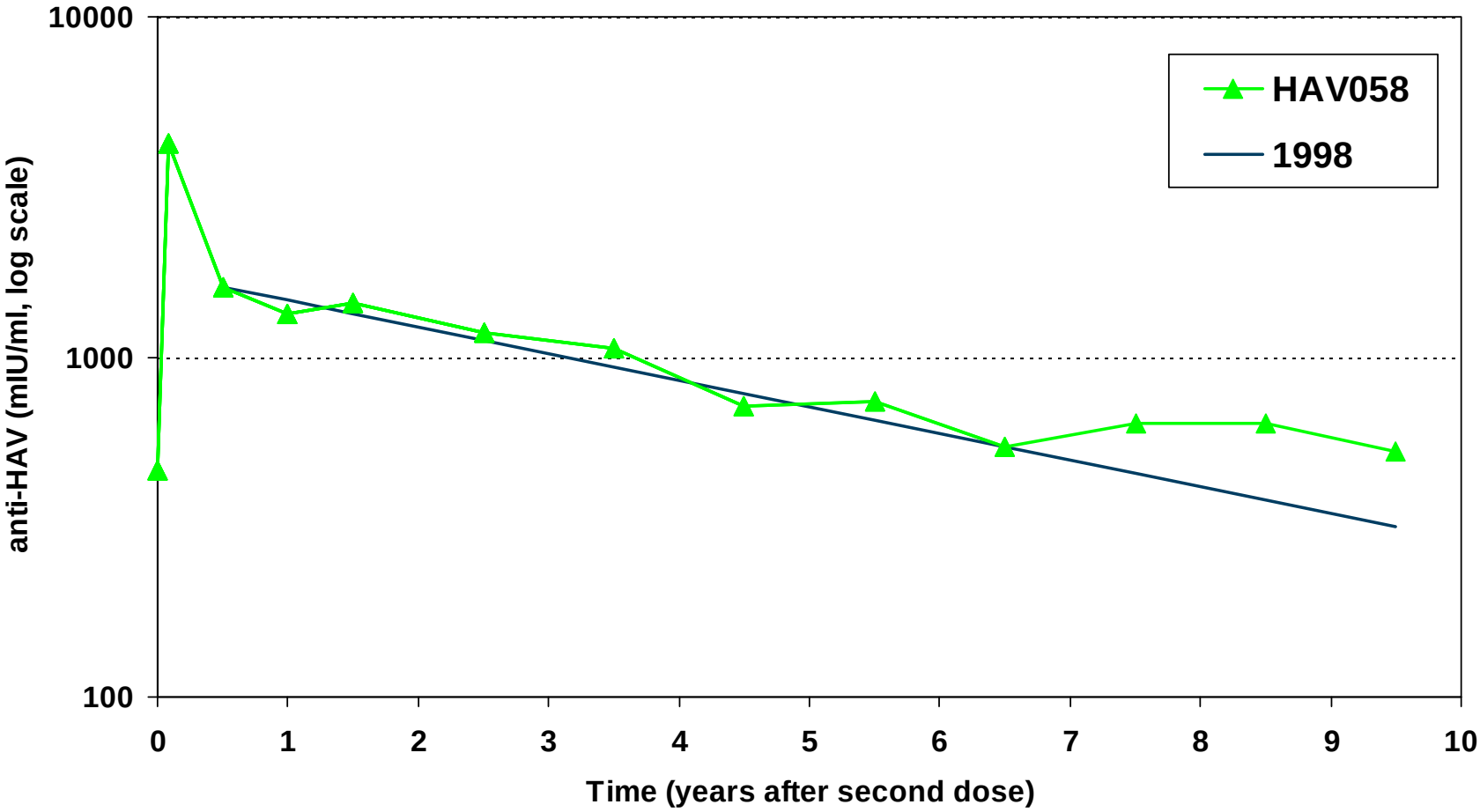
AB persistence: hepatitis A
Linear extrapolation (1994-2001)



Van Damme et al, J Med Virol 1994

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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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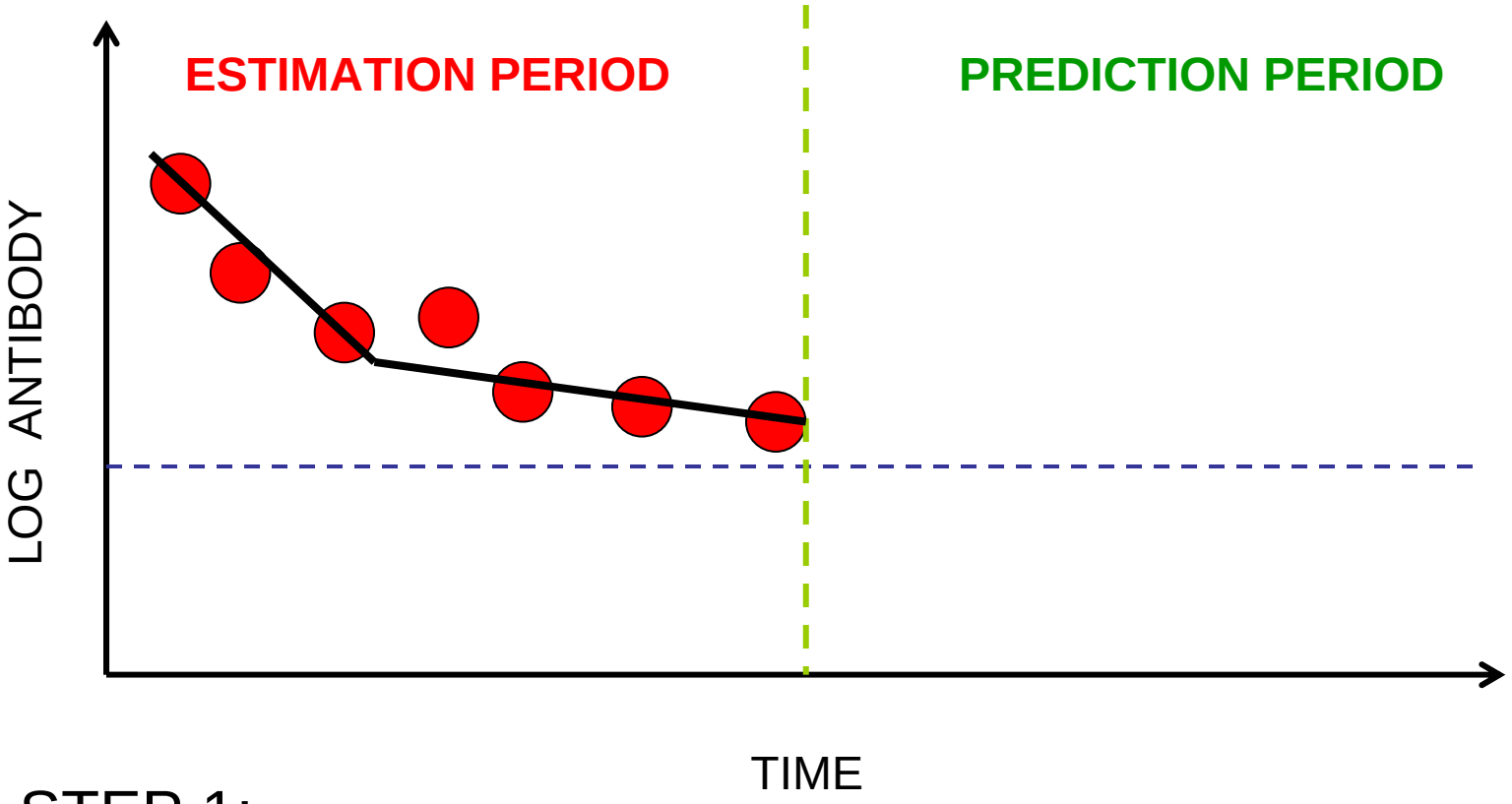
Estimation Period



STEP 1:

Modeling the change in antibody level in the estimation period

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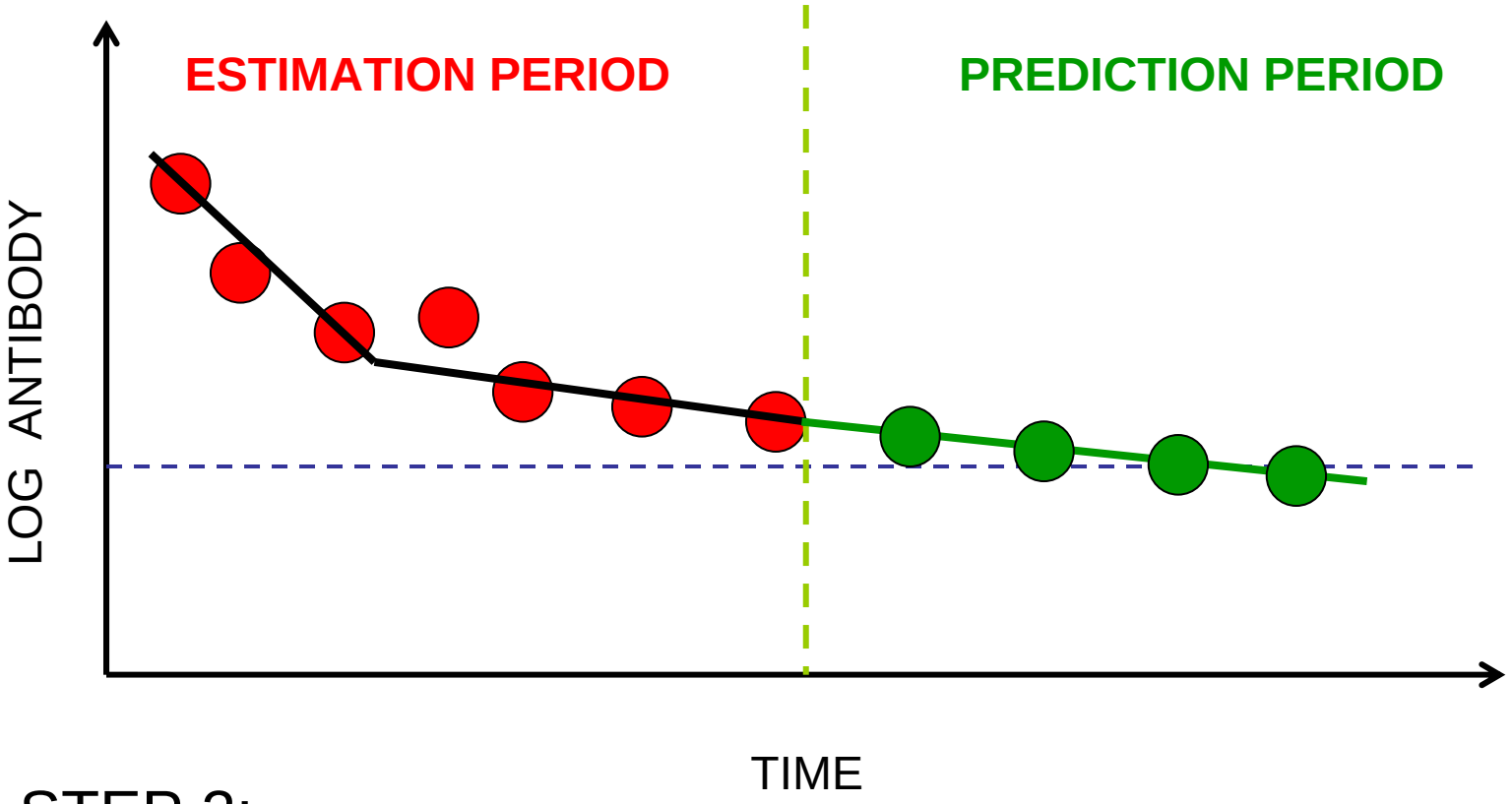
Results

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

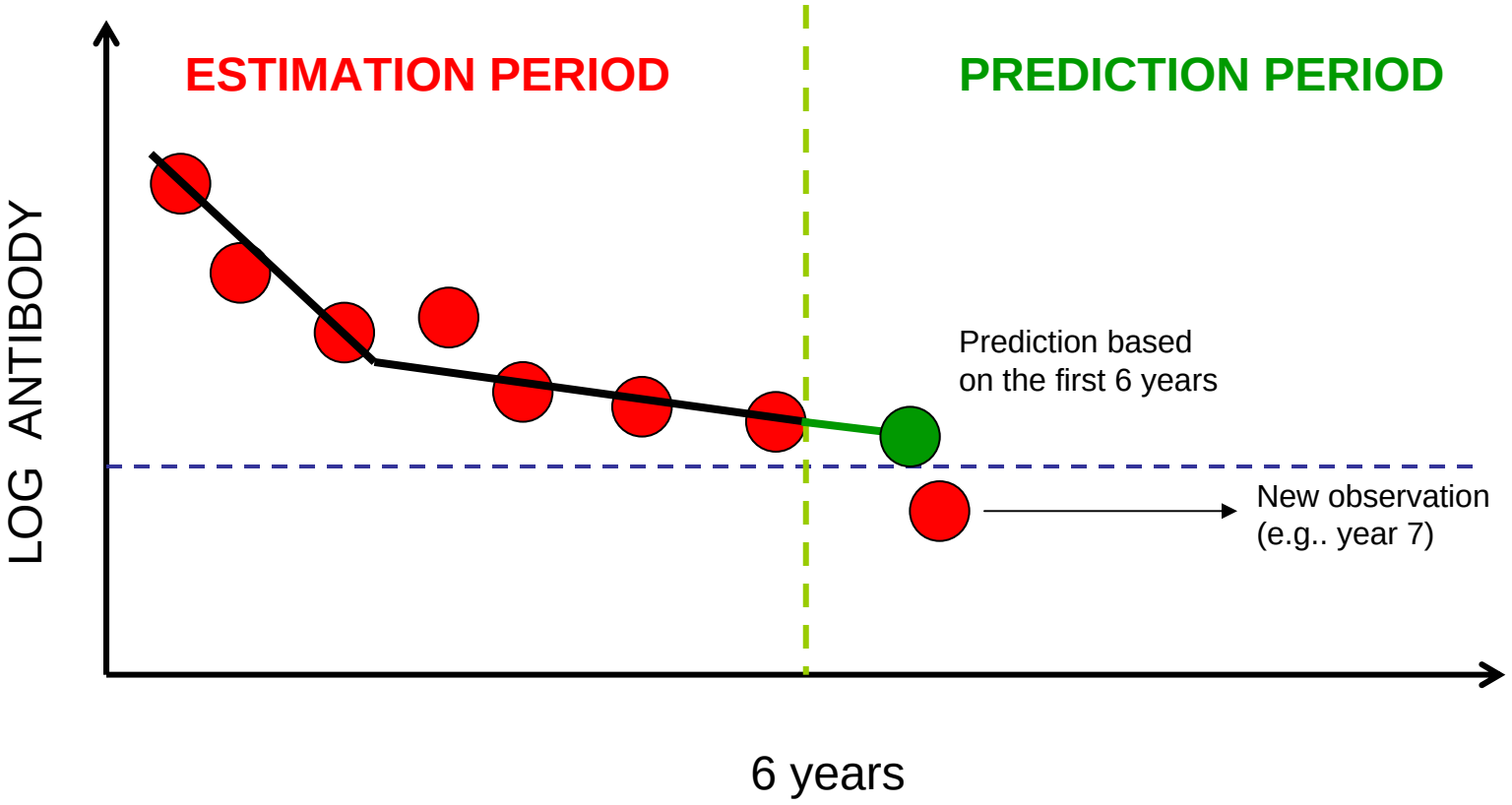
Long-Term Predictions



STEP 2:

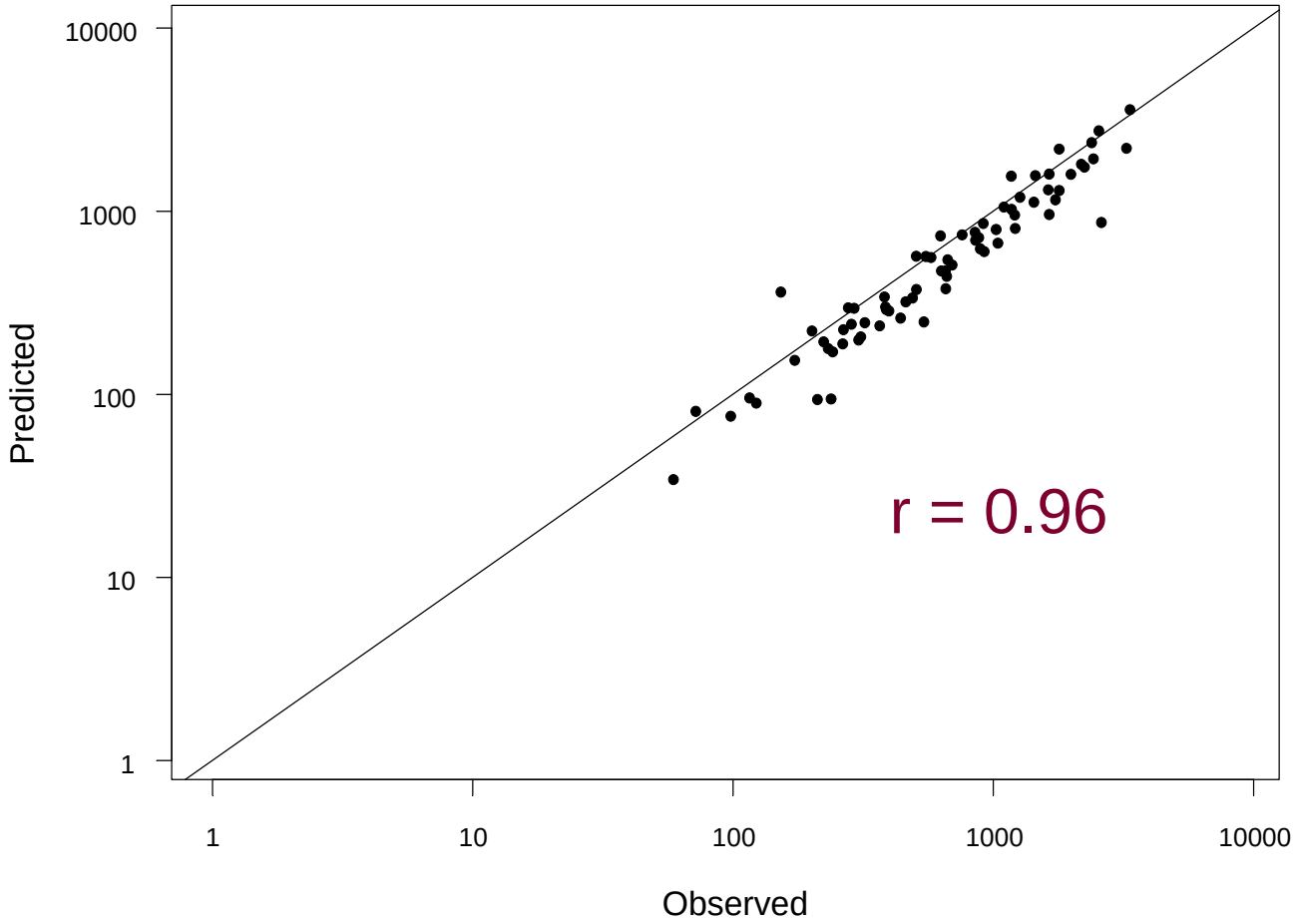
Long term prediction

First Step: Validation of the model

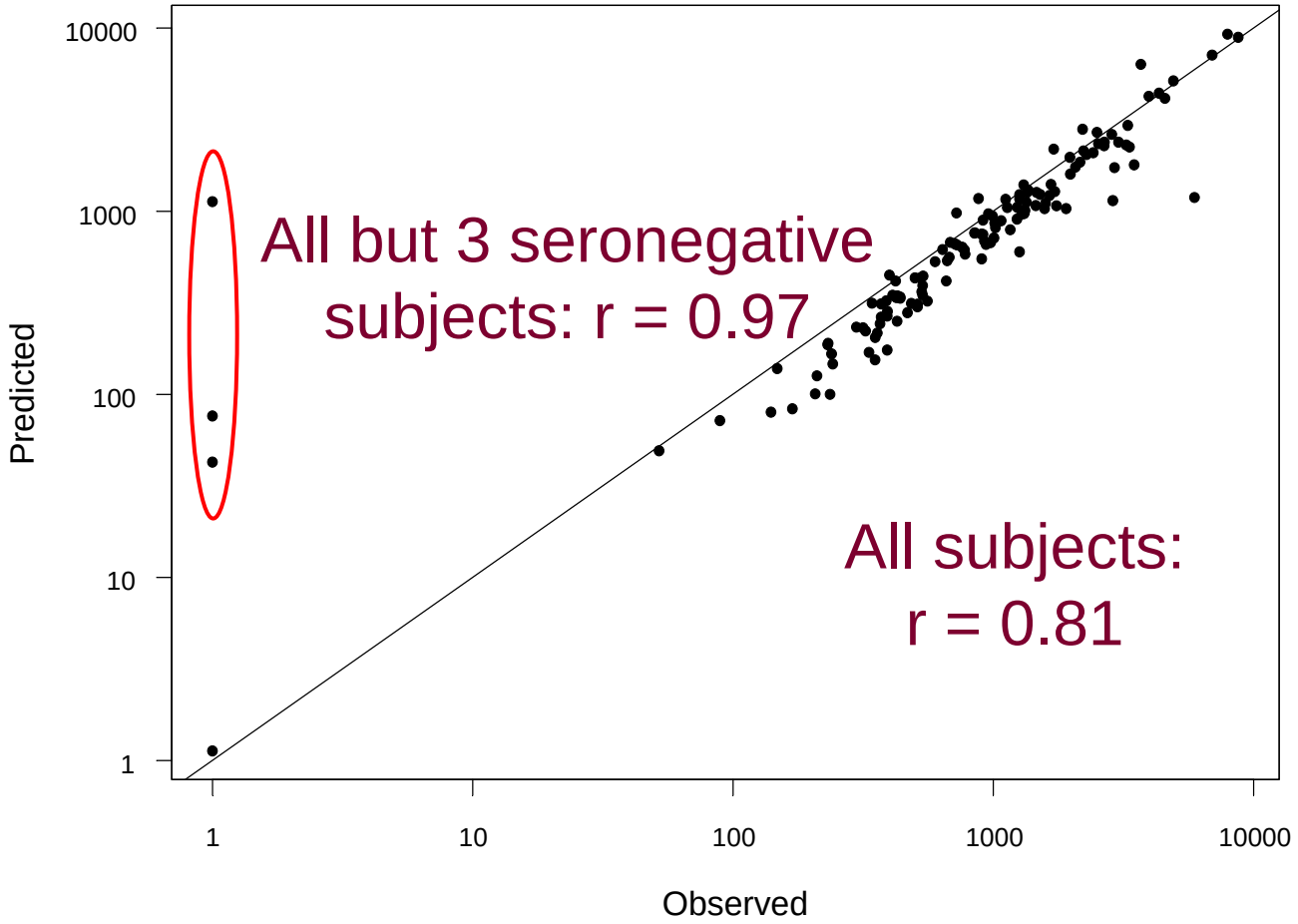


Correlation between the predicted value at 7 years (based on 6 years data) and the observed value.

HAV123 (0-6): correlation



HAV112 (0-12): correlation



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

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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

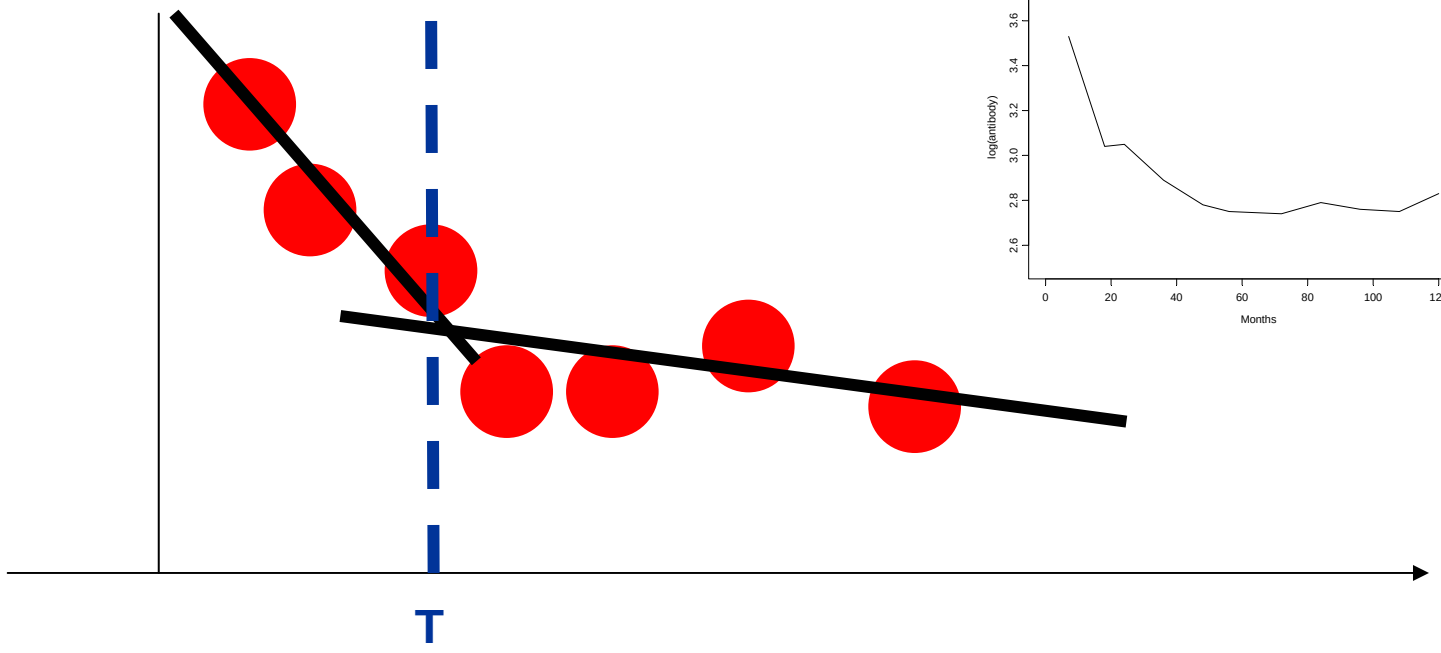
Mean Structure (1): linear model with a change point

For $t_j < T$:

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

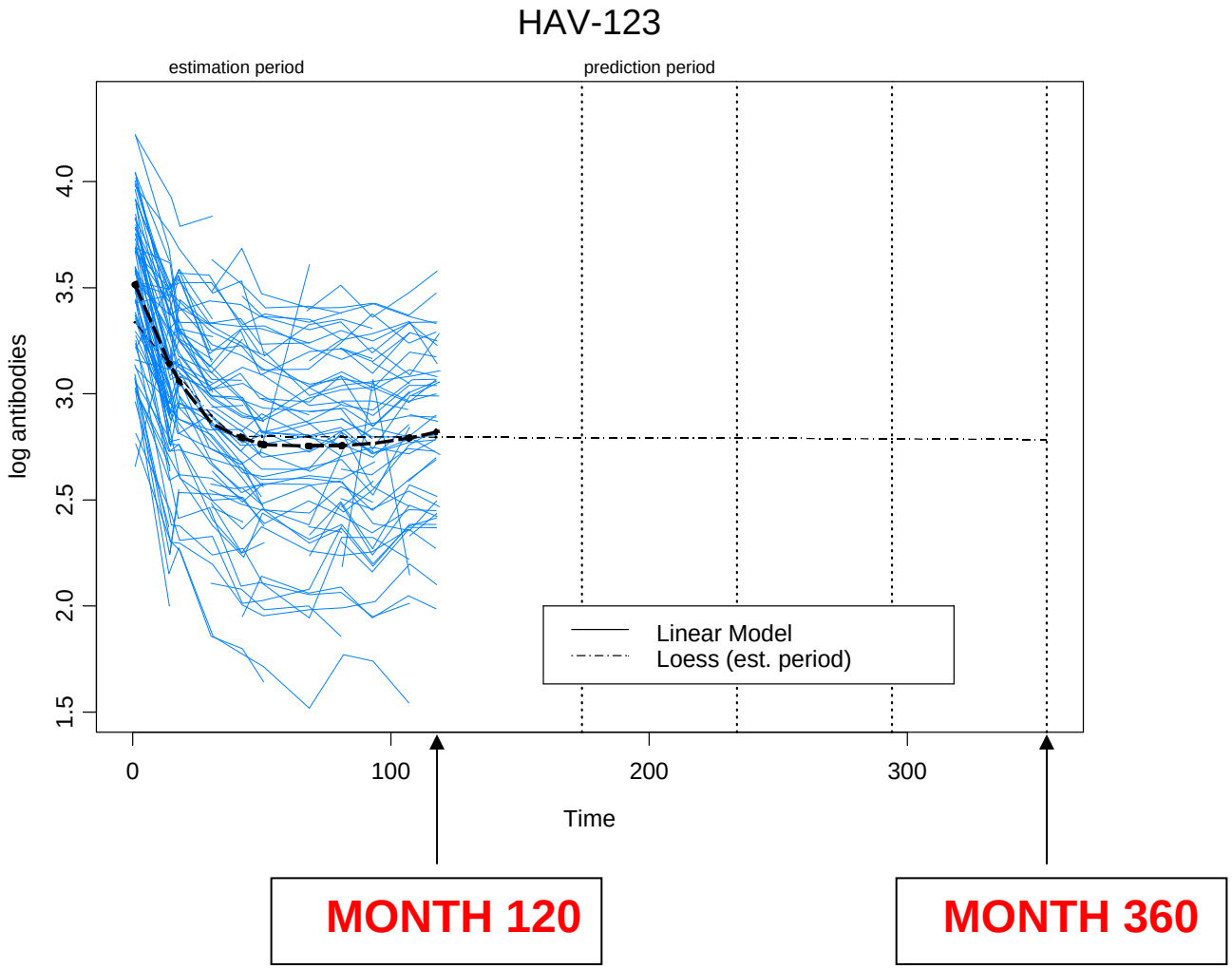
For $t_j >= T$:

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



- We allow for a change in linear trend.

Second Step:
Long-Term Predictions



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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

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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

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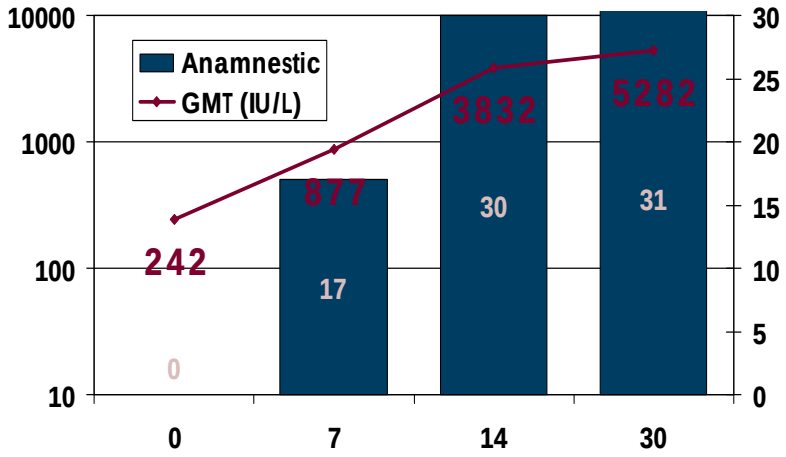
Indirect evidence: booster study



- 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

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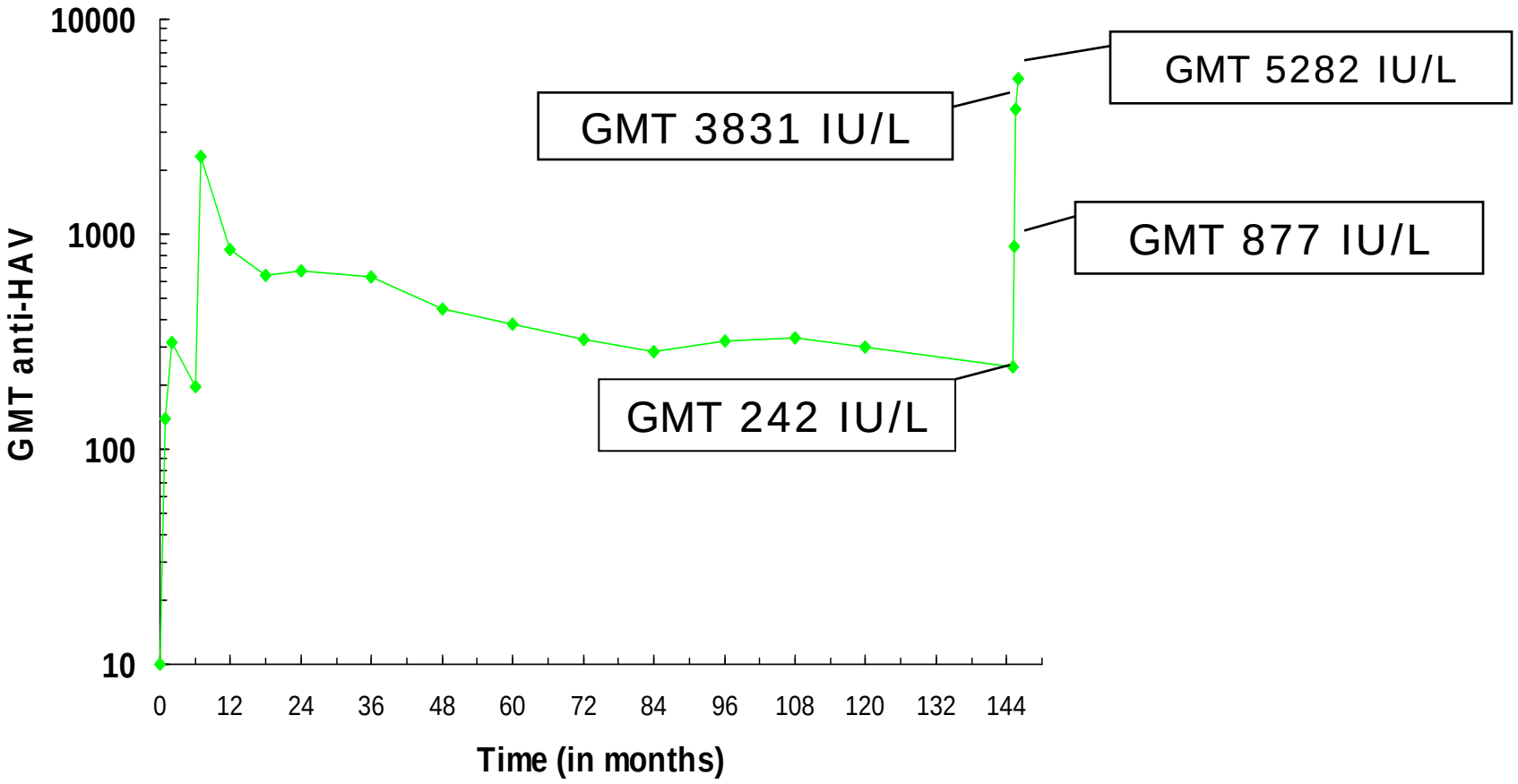
follow-up Month 145



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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?

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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

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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

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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