Vaccine & Infectious Disease Institute

Centre for the Evaluation of Vaccination

Miami, 30/11/2007

Hepatitis A:
performance of the available vaccines

Koen Van Herck, MD, PhD

Centre for the Evaluation of Vaccination

Vaccine & Infectious Disease Institute

University of Antwerp

Belgium

Universiteit Antwerpen

Centre for the Evaluation of Vaccination

Performance of hepatitis A vaccines: HEpatitis FLoridA

- Highly immunogenic
  - No non-response
  - Rapid seroconversion
  - Long-term antibody persistence
- Excellent safety profile
- Freedom to choose
  - Coadministration / combination vaccines
  - Flexible vaccination schedule
  - Interchangeability
- Long-lasting protection
  - Beyond antibody persistence (life-long)
  - Proven effectiveness, even post-exposure
- After single dose? How long protected?

Centre for the Evaluation of Vaccination

Available vaccines (1)

- Vaccines widely available
  - Avaxim (0 / 6-12 months)
    - GBM strain
    - Sanofi Pasteur, Lyon, France
  - Epaxal (0 / 6-12 months)
    - RG SB strain
    - Berna Biotech Ltd, Bern, Switzerland
  - Havrix (0 / 6-12 months)
    - HM 175 strain
    - GlaxoSmithKline Biologicals, Rixensart, Belgium
  - Vaqta (0 / 6-18 months)
    - CR326F strain
    - Merck & Co, West Point, PA, USA

Centre for the Evaluation of Vaccination

Available vaccines (2)

- Vaccines with more limited distribution
  - Chinese live attenuated vaccine
    - H2 strain
    - Zhejiang Academy of Medical Sciences, Hangzhou, People's Republic of China
  - Vietnamese vaccine
    - Vaccine and Bio-product Company 1, Vietnam
  - Nothav
    - Chiron Behring GmbH, Italy
  - Locally produced vaccines in
    - Russia, Brazil, ...?

Centre for the Evaluation of Vaccination

Combination vaccines

- Hepatitis A and B
  - Twinrix (0 / 1 / 6 months)
  - Ambirix (0 / 6 months)
    - GlaxoSmithKline Biologicals, Rixensart, Belgium
  - Chinese vaccine
- Hepatitis A and typhoid fever
  - Hepatyrix
    - GlaxoSmithKline Biologicals, Rixensart, Belgium
  - Viatim
    - Sanofi Pasteur, Lyon, France

Centre for the Evaluation of Vaccination

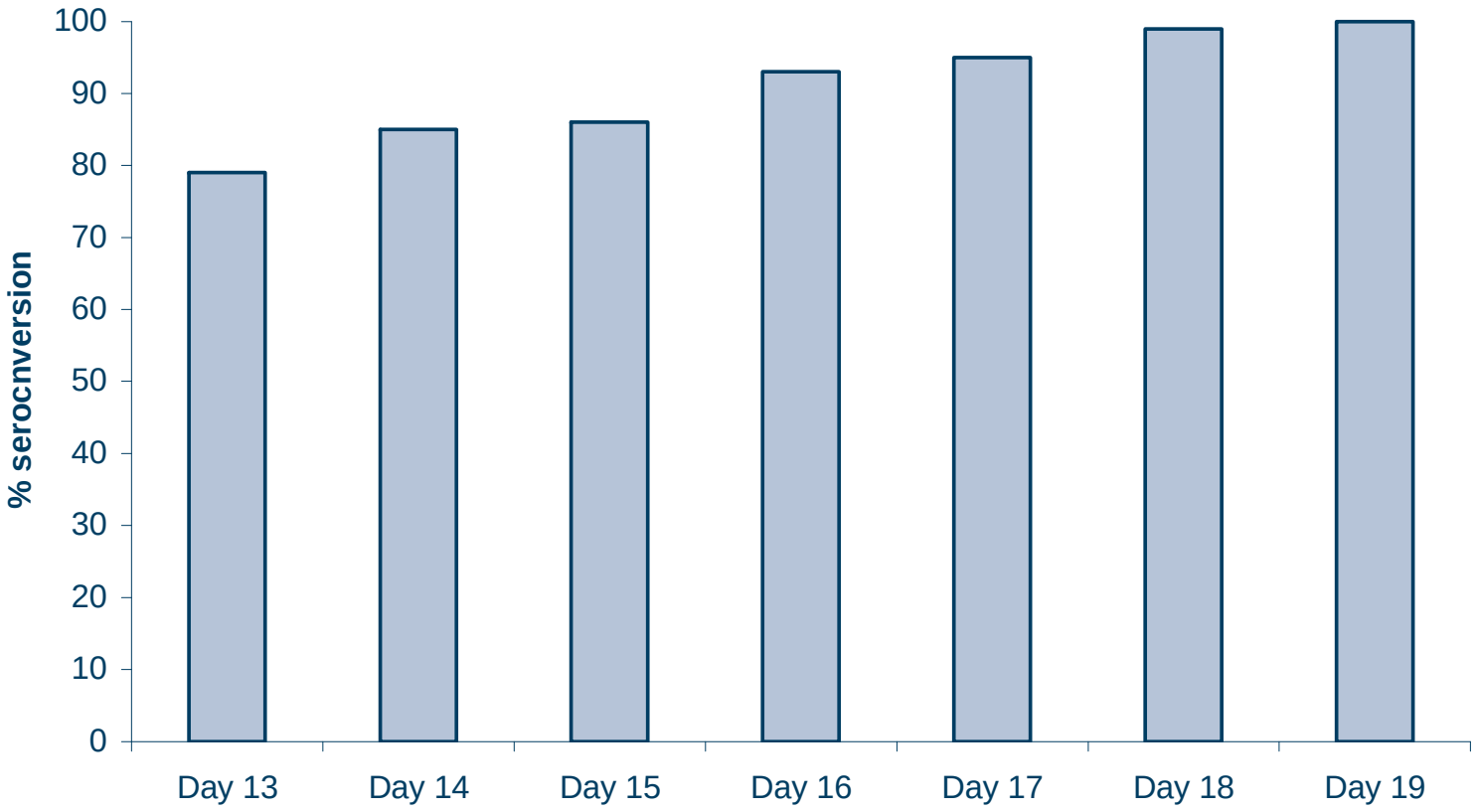
Immunogenicity (1)

- Highly immunogenic
  - No non-response (virtually)
    - Few cases reported
  - Rapid seroconversion
    - For all vaccines
      - Inactivated: 95-100% after 2-4 weeks
      - Live vaccine: 95% after 2-5 weeks
    - Allows immunization of travellers up to departure

Ambrosch, Infection 2004; Connor, Biodrugs 2003; Vidor, Eur J Clin Microbiol Infect 2004

Centre for the Evaluation of Vaccination

Rapid seroconversion



Connor, Biodrugs 2003

Centre for the Evaluation of Vaccination

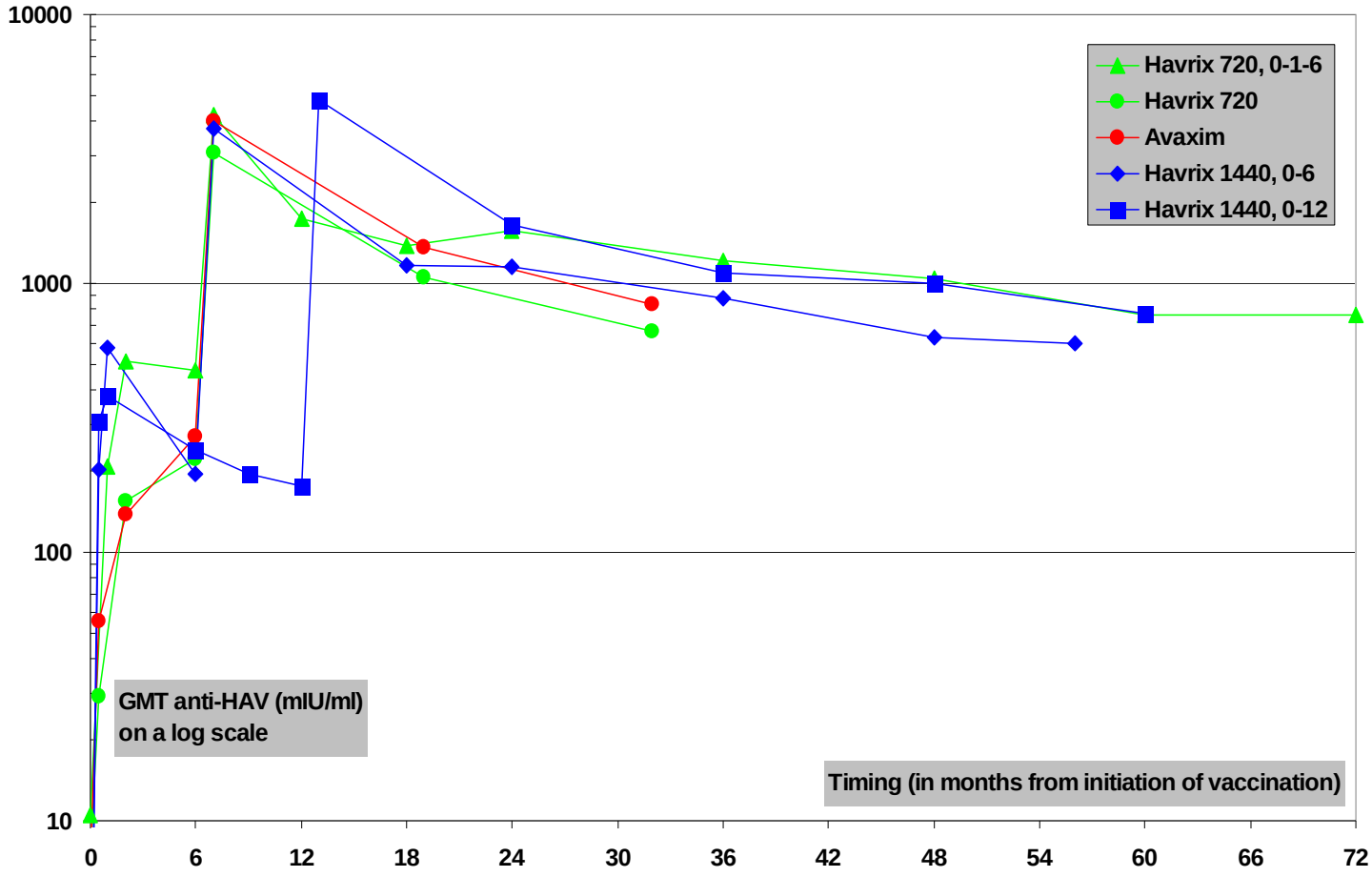
Immunogenicity (2)

- Highly immunogenic
  - Long-term persistence of antibodies
    - Detectable antibodies: many years after completion of vaccination schedule
      - hardly any subjects lose their antibodies
        - » children: up to 11 years
        - » adults: up to 10 years, and still ongoing
      - also in unselected populations
        - » >1000 fully vaccinated travellers
        - » blood sample ±10 years later
        - » 98% still had anti-HAV ≥10 IU/L

Bovier 2002; Fan 1998; Chan 1999; Hammitt (AASLD) 2007; 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

Centre for the Evaluation of Vaccination

Long-term anti-HAV persistence
Observed long-term results in adults



Hepatitis A Vaccine: Immunogenicity Through 11 Years

Age Group at Vaccination	Dose Schedule (Months)	Percent Anti-HAV > 20 mIU
Children Ages 3 to 6 yrs	0, 1, 2	91%
Children Ages 3 to 6 yrs	0, 1, 6	100%
Children Ages 3 to 6 yrs	0, 1, 12	100%
Adults	0, 1, 12	96%

Hammitt (AASLD) 2007 – courtesy of B. McMahon

Centre for the Evaluation of Vaccination

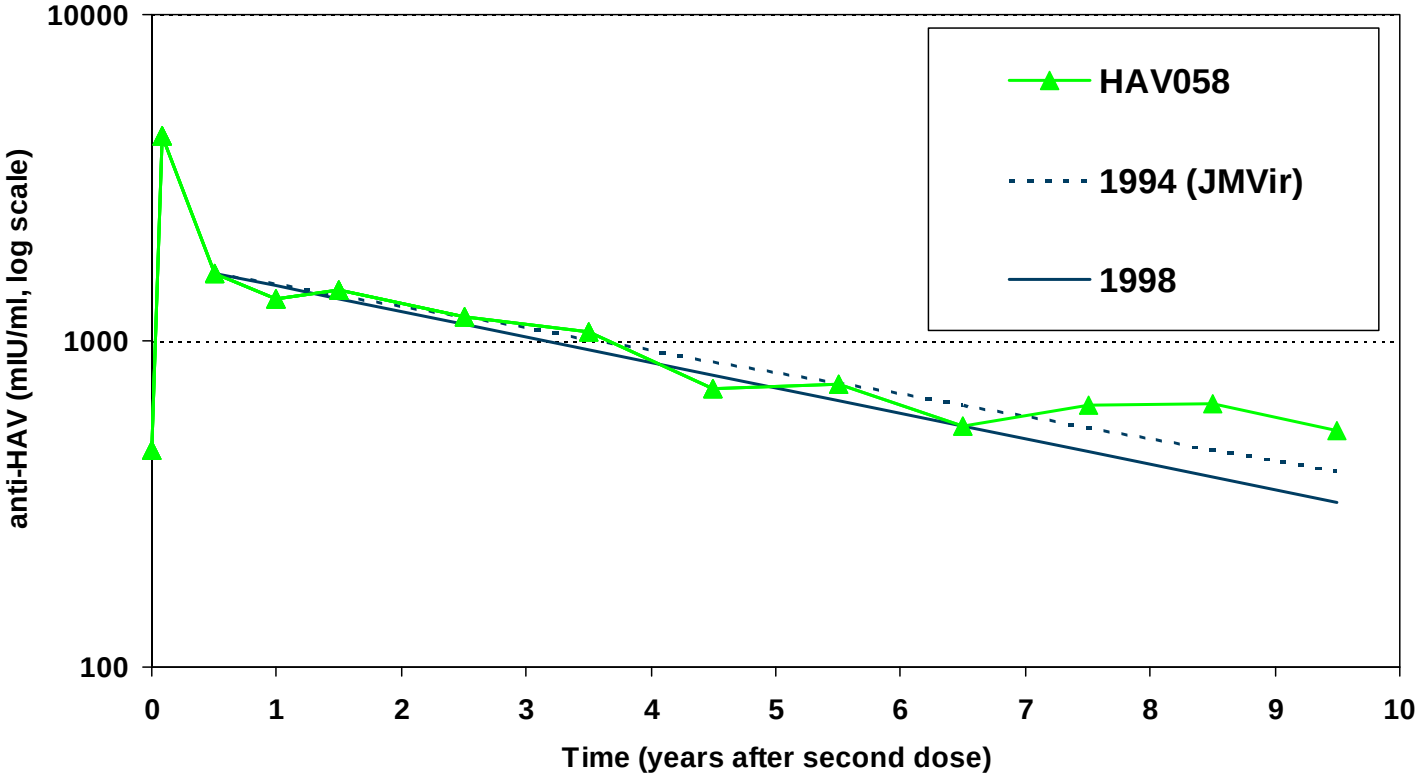
Immunogenicity (3)

- Highly immunogenic
  - Long-term persistence of antibodies
    - Detectable antibodies: many years after completion of vaccination schedule
      - hardly any subjects lose their antibodies
        - » children: up to 11 years
        - » adults: up to 10 years, and still ongoing
      - Also in unselected populations
  - Log-linear extrapolation method (average persistence)
    - children: 14-25 years
    - adults: 20-25 years

Bovier 2002; Fan 1998; Chan 1999; Hammitt (AASLD) 2007; 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

Centre for the Evaluation of Vaccination

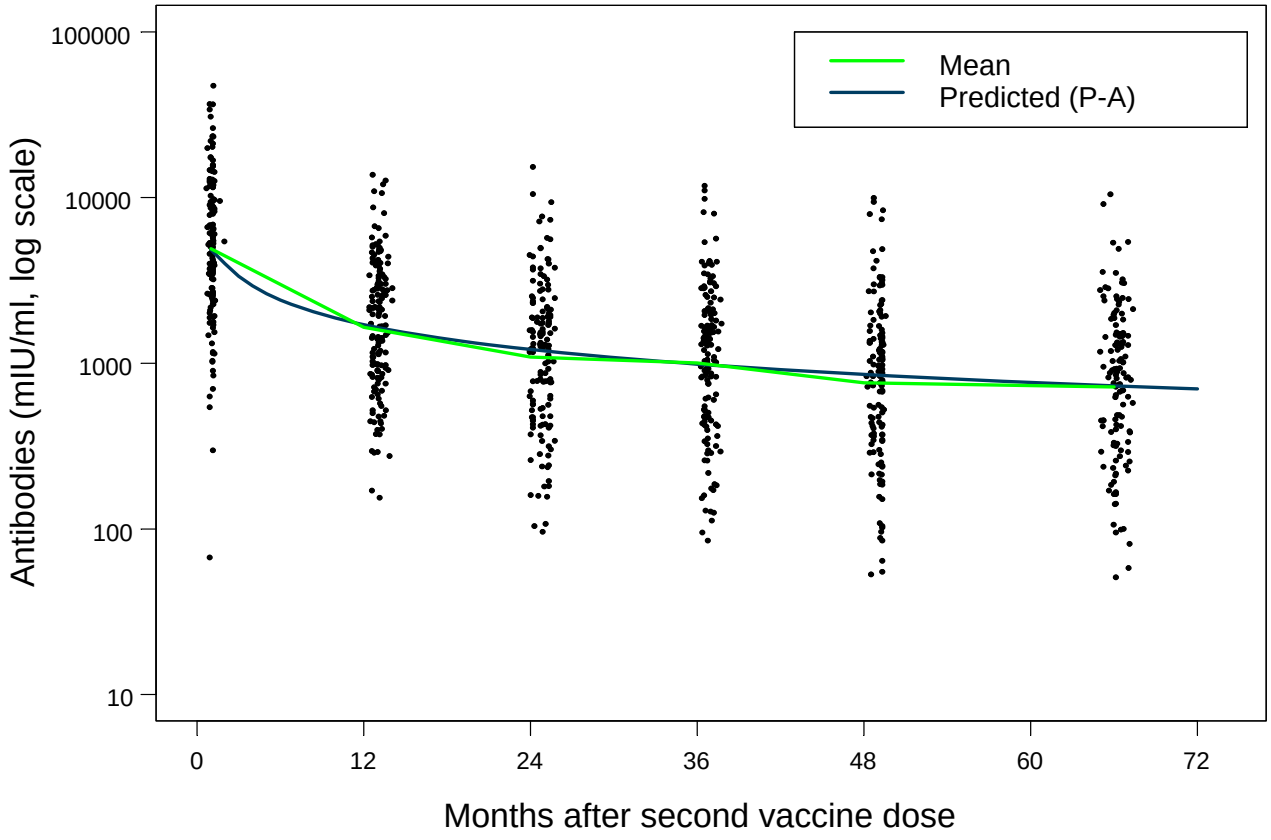
AB persistence: hepatitis A
Linear extrapolation (1994-2001)



Van Damme et al, J Med Virol 1994

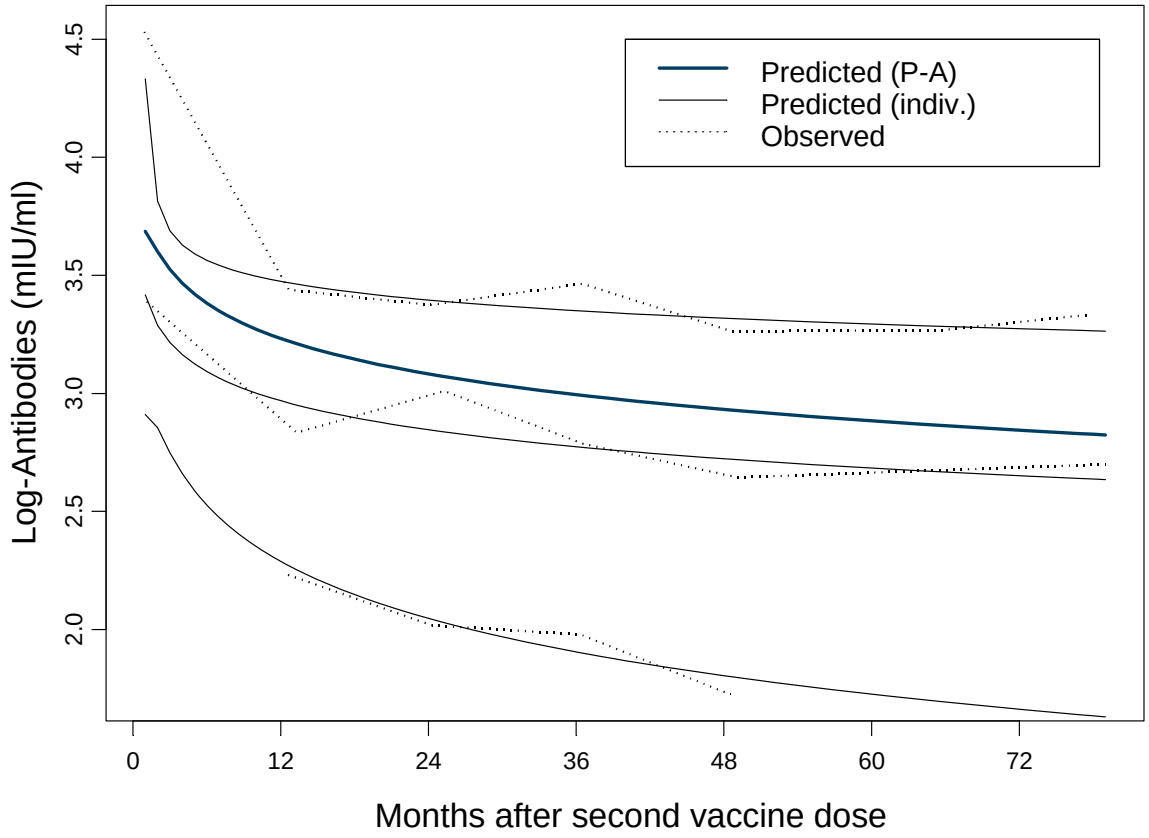
Centre for the Evaluation of Vaccination

Hepatitis A: Linear mixed model Population-based



Centre for the Evaluation of Vaccination

Hepatitis A: Linear mixed model Individual based



Centre for the Evaluation of Vaccination

Hepatitis A: Linear mixed model Long-term estimates

- Individual predictions after 25 years
  - 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 %
- Similar results with other vaccines

Bovier 2002; Bovier 2005; Pigeon 1999; Van Herck (ISVHLD) 2000

Centre for the Evaluation of Vaccination

Immunogenicity (3)

- CAVE: 1st year of life (maternal ABs)
  - Reduced humoral immune response
  - BUT: adequate priming and immune memory
    - Robust anamnestic response to booster dose
    - Even up to 6 years post-vaccination

Fiore, PIDJ 2003; Kanra, Turk J Pediatr 2000; Kanra, PIDJ 2002; Letson, J Pediatr 2004; Lopez, Vaccine 2007; Piazza, Vaccine 1999; Troisi, Vaccine 1997; Usonis, Vaccine 2003; Vidor 2007

Centre for the Evaluation of Vaccination

Safety and tolerability

- Excellent safety profile
  - Mild and transient local site reactions
    - children 20%, adults 50%
      - pain
      - swelling
      - redness
    - Epaxal compared to alum-adsorbed vaccines
      - 2-3 times lower rate of local reactions
  - General reactions
    - reported in <5% of vaccinees
      - fever, fatigue, diarrhoea, vomiting, headache

André, Expert Rev Vaccines 2002; Black, Vaccine 2004; Bovier, Vaccine 2005; WHO, WER 2000; Zuckerman, Adv Ther 1997

Centre for the Evaluation of Vaccination

Freedom to choose

- Co-administration possible
  - Paediatric: DT(a)P; OPV/IPV; Hib; hepatitis B
  - Travellers: hepatitis B, polio, dT, typhoid fever, yellow fever, rabies, cholera, Jap. Encepalitis
- Combination vaccines (hepB, typhoid fever)
- Flexible vaccination schedule
  - 0 + 6-12 (6-18) months, and beyond
- Interchangeability
  - Not all combinations tested
  - Existing studies show similar results

Bovier, Vaccine 2005; Bryan, Vaccine 2001;
Van Herck, Expert Rev Vaccines 2005; Vidor, Eur J Clin Microbiol Infect 2004

Centre for the Evaluation of Vaccination

Long-lasting protection (1)

- CAVE:
  - Minimal protective level not 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

Centre for the Evaluation of Vaccination

Protective efficacy (1)

- Efficacy trials
  - Epaxal: 100%
    - Nicaragua, 274 children (1.5 - 6 yo)
  - Havrix: 95%
    - Thailand, >40,000 children (1-16 yo)
  - Vaqta: 100%
    - USA (Monroe), >1,000 children (2-16 yo)
  - Chinese live vaccine: 95%
- Also in post-exposure prophylaxis
  - Outbreak control

Innis, JAMA 1994; Perez, J Infect Dis 2003; Werzberger, NEJM 1992; Zhao 2000

Centre for the Evaluation of Vaccination

Field effectiveness

- Well-demonstrated in a number of mass vaccination programmes
  - massive reduction in disease incidence
    - in targeted AND in other age groups
    - to what extent due to vaccination?
  - different settings
    - targeted age group, vaccination schedule, vaccine, coverage, …
    - US, Israel, Australia, Italy, Spain
    - Argentina, Belarus, China, …

Dagan 2005; Lopalco 2001; Dominguez 2003; MacIntyre 2003; Van Damme 2005; Wasley 2005; Zhuang 2005

Centre for the Evaluation of Vaccination

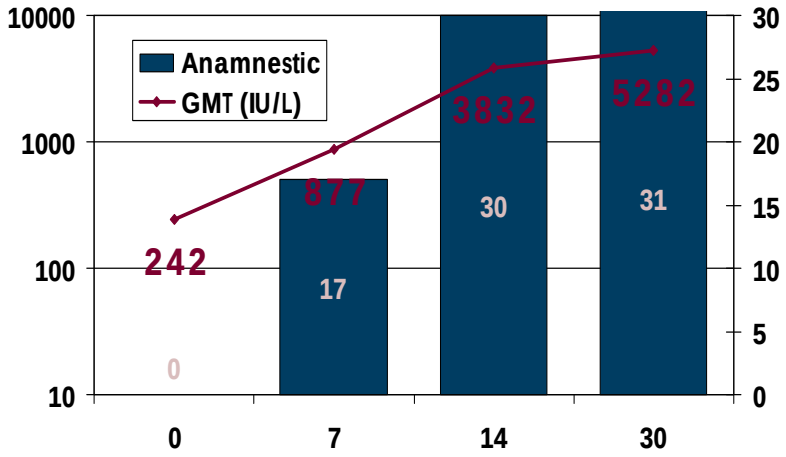
Long-lasting protection (2)

- 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, Vaccine 1992

Centre for the Evaluation of Vaccination

Indirect evidence: booster study

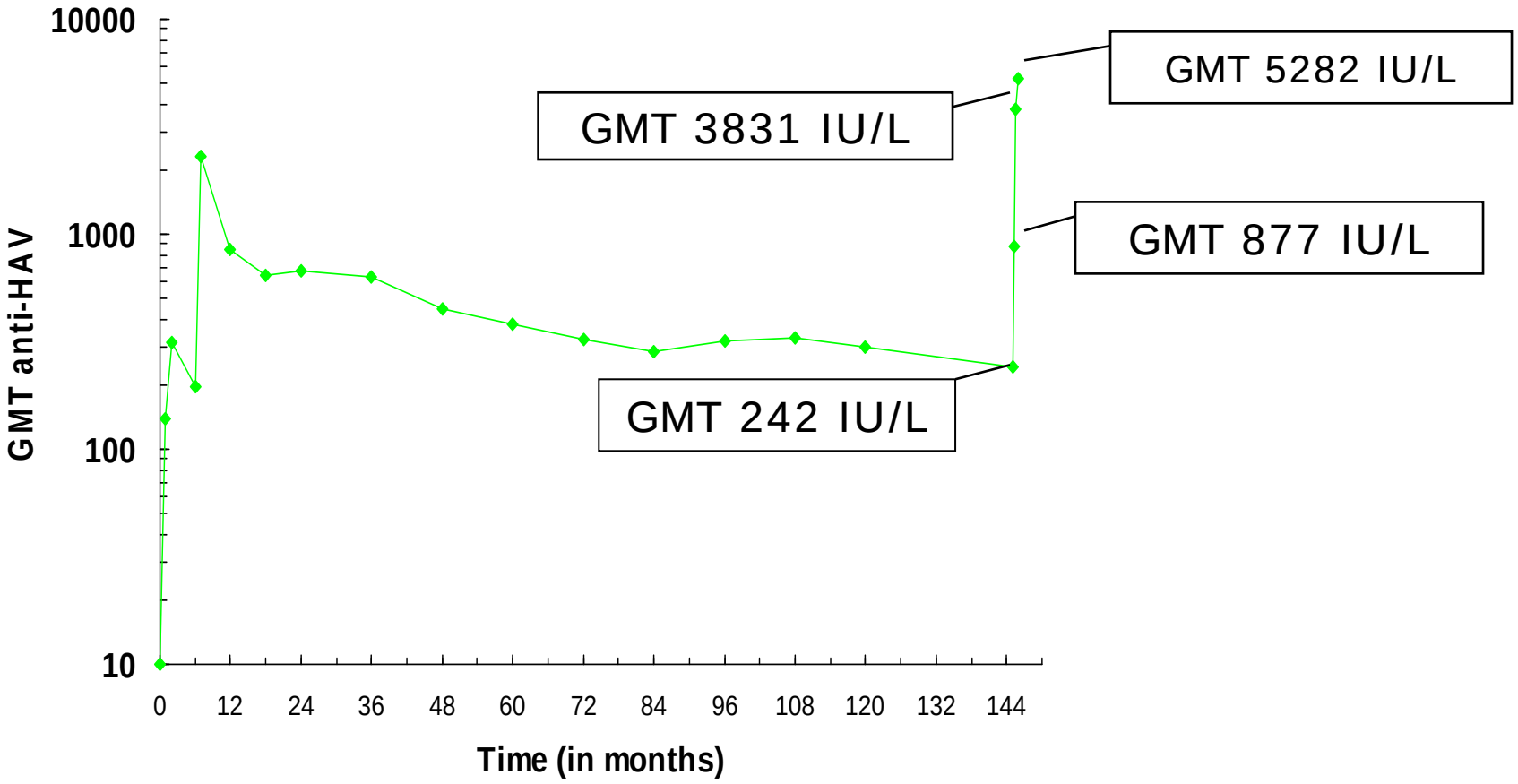


- 12 years since Havrix 720 (0-1-6)
- Cohort (N=150) followed for 10 years
- Booster study: n=31
- Booster: Havrix 720
- Anamnestic response
  - titre at least x2 (or x4 if <100 IU/L at day 0)
- Day 0: 100% seropositive
- Fast, strong response within 2 weeks

Van Herck 2004

Centre for the Evaluation of Vaccination

follow-up Month 145



Centre for the Evaluation of Vaccination

HAV: consensus on boosters

- NO booster required if:
  - fully vaccinated
  - normal immune system
    - persistence of antibodies (observed + modelled)
    - persistence of immune memory
      - delayed 2nd dose – excellent response, even after antibody loss
      - booster study 2002
    - rely on immune memory
      - except: immunocompromised (lack of data)
- Also for combination vaccines

Van Damme, Lancet 2003

Centre for the Evaluation of Vaccination

HAV consensus
Special patient groups

- Data available for patients with CLD, chronic HBV infection, chronic HCV infection, HIV
  - Generally comparable to lower seroconversion rates and lower antibody concentrations but protection against HAV infection can be achieved
  - Success of seroconversion in HIV-positive individuals was related to their CD4+ count
    - 2005 meta-analysis: 64% [52-75%] response rate
  - Further studies on persistence of antibodies needed before booster recommendations can be developed

Keeffe 1998; Lee 1997; Neilsen 1997; Shire 2005

Centre for the Evaluation of Vaccination

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

Centre for the Evaluation of Vaccination

Conclusions: HEpatitis FLoridA

- Highly immunogenic
  - No non-response
  - Rapid seroconversion
  - Long-term antibody persistence
- Excellent safety profile
- Freedom to choose
  - Coadministration / combination vaccines
  - Flexible vaccination schedule
  - Interchangeability
- Long-lasting protection
  - Beyond antibody persistence (life-long)
  - Proven effectiveness, even post-exposure
- After single dose? How long protected?