Technical Viral Hepatitis Prevention Board Meeting - Milan, Italy Nov 17-18 2011

Hepatitis B vaccination: a completed schedule … enough to control HBV lifelong?

Humoral and cellular immune responses after hepatitis B (booster) vaccination. How long will immune memory last?

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Immune memory

cardinal feature of the *adaptive* immune system:

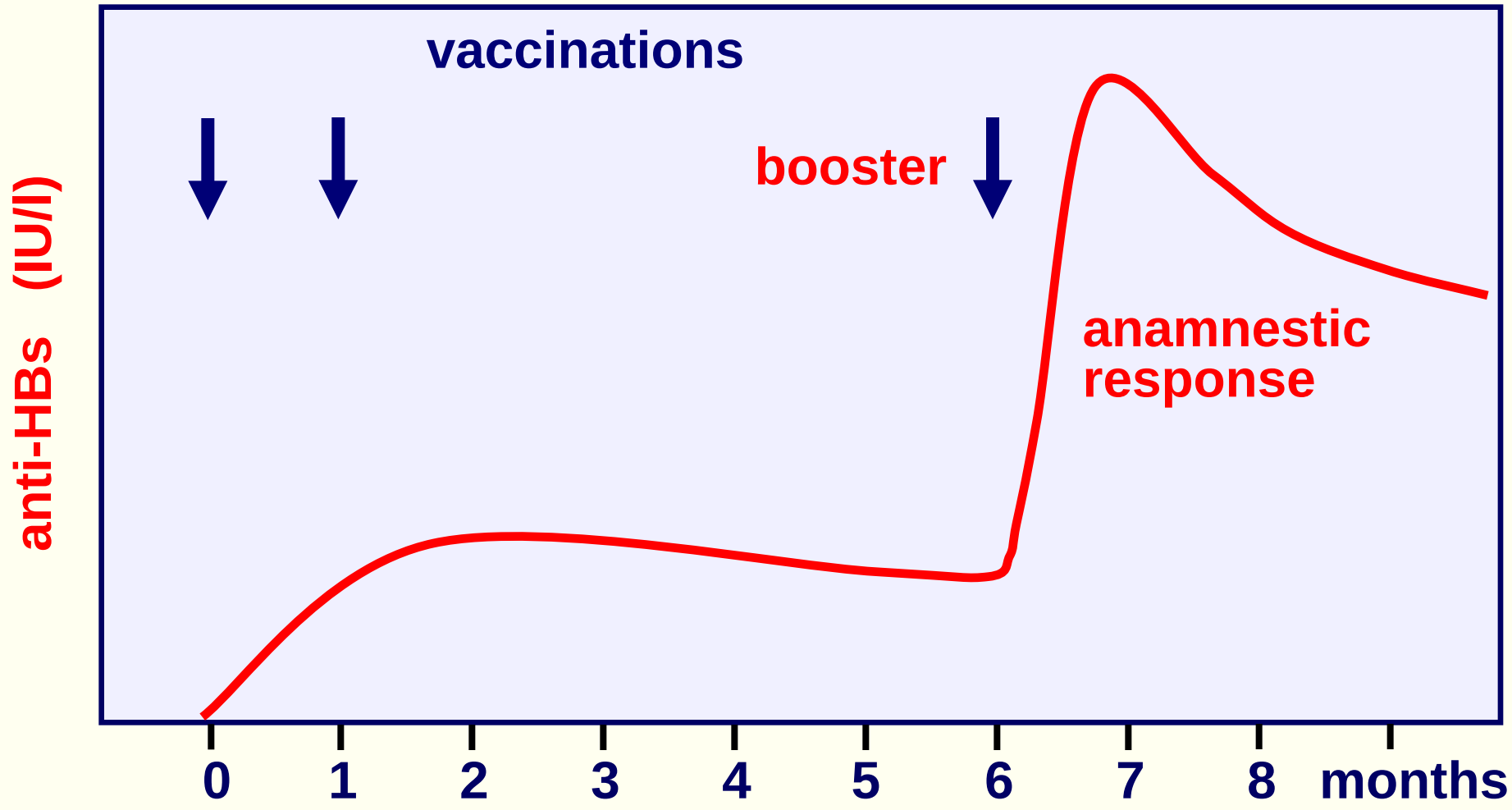
- **ability to maintain protective level of specific antibody by *long-lived plasma cells***
- **ability to mount an *accelerated* immune response upon re-exposure to the same pathogen *(anamnestic response) due to generation of memory B- and T-cells***

How can immune memory be demonstrated?

- epidemiologically: prevention of reinfection or disease
- persistence of specific antibodies in the protective range
- „boostability“ of specific antibodies by revaccination
- demonstration of memory T- and B-cells

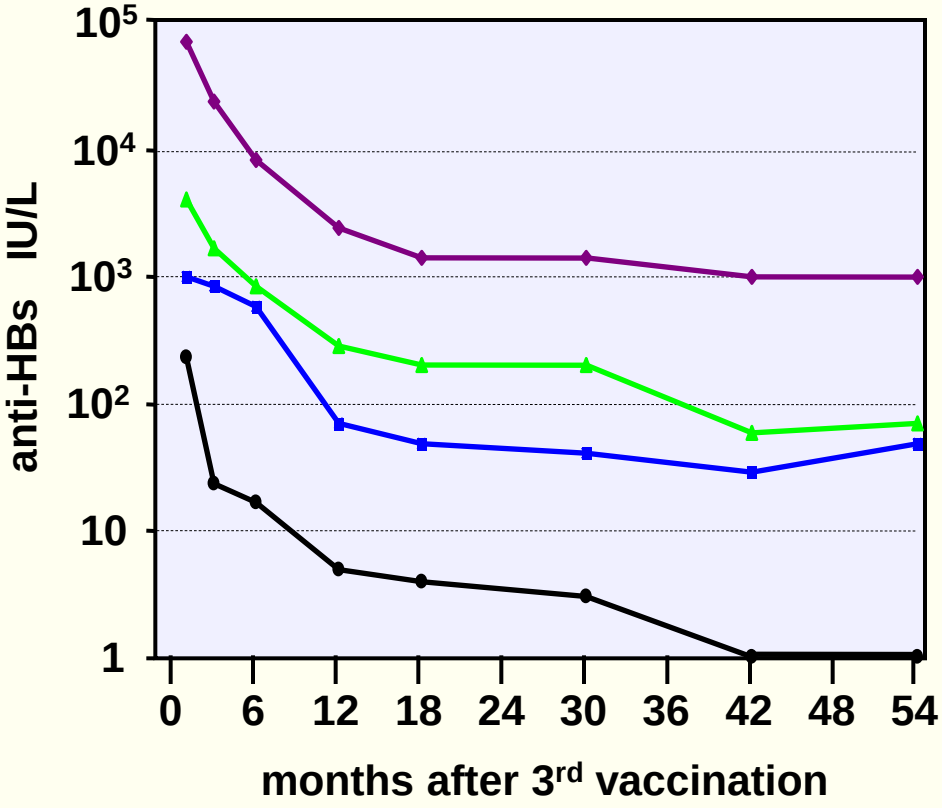
Vaccination against Hepatitis B:

generation of specific antibodies



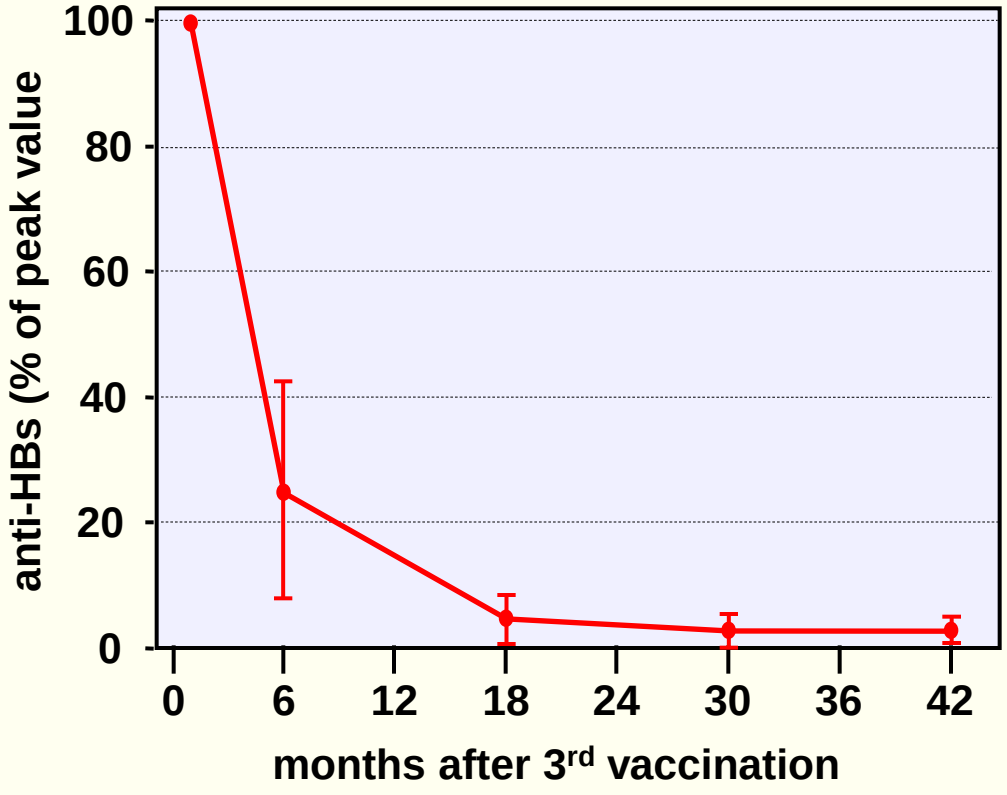
Decrease of anti-HBs after hepatitis B vaccination

course of anti-HBs in 4 vaccinees



Jilg et al, Lancet 1990; 335:173

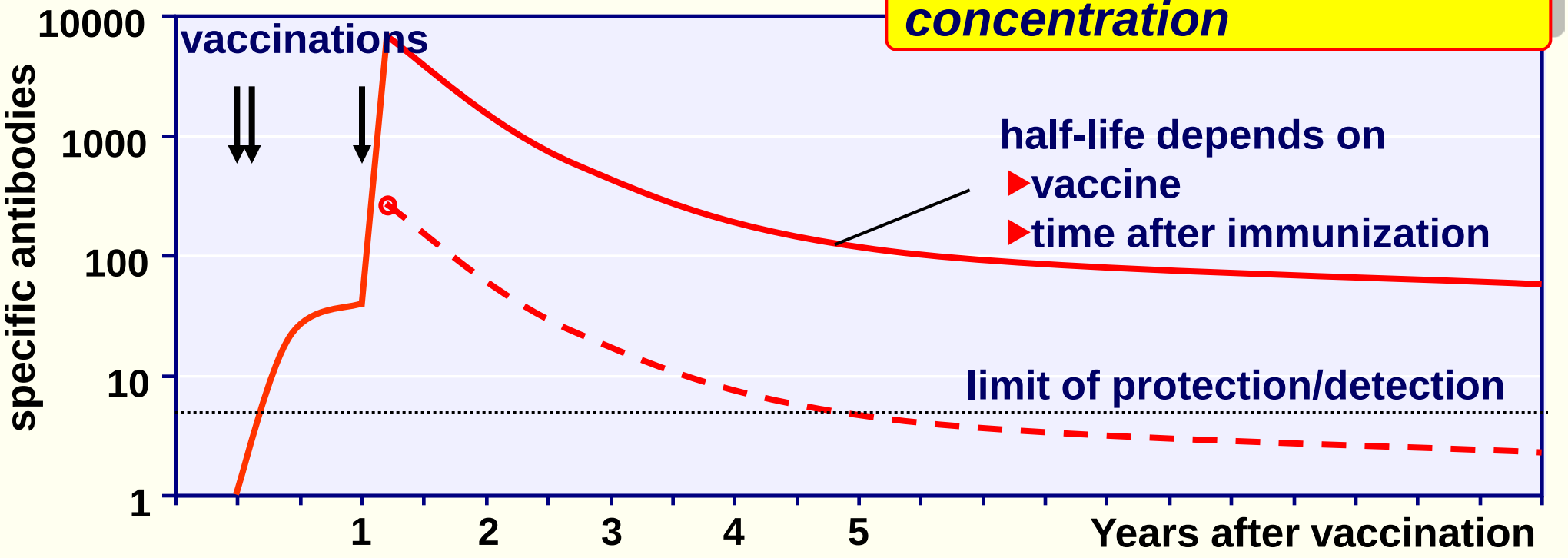
percentage decrease of anti-HBs (mean of 202 vaccinees)



Jilg et al, Infection 1989;17:70-76

Kinetics of specific antibodies after vaccination with protei

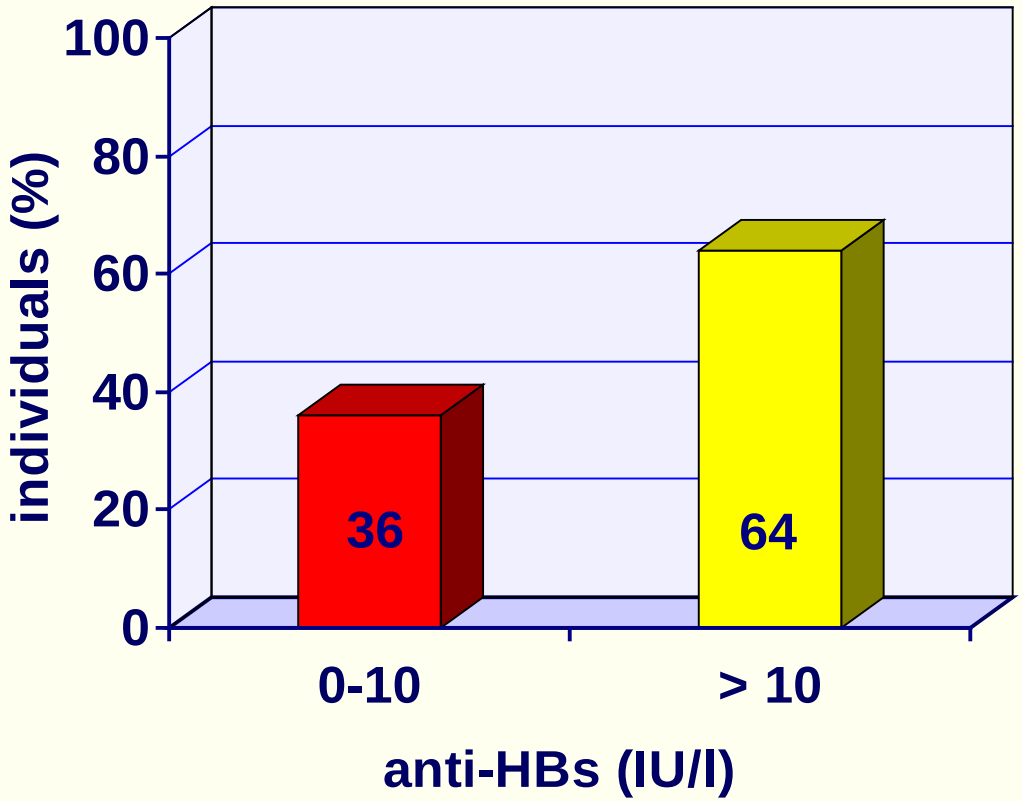
Persistence of specific antibodies above a certain limit is a function of peak concentration



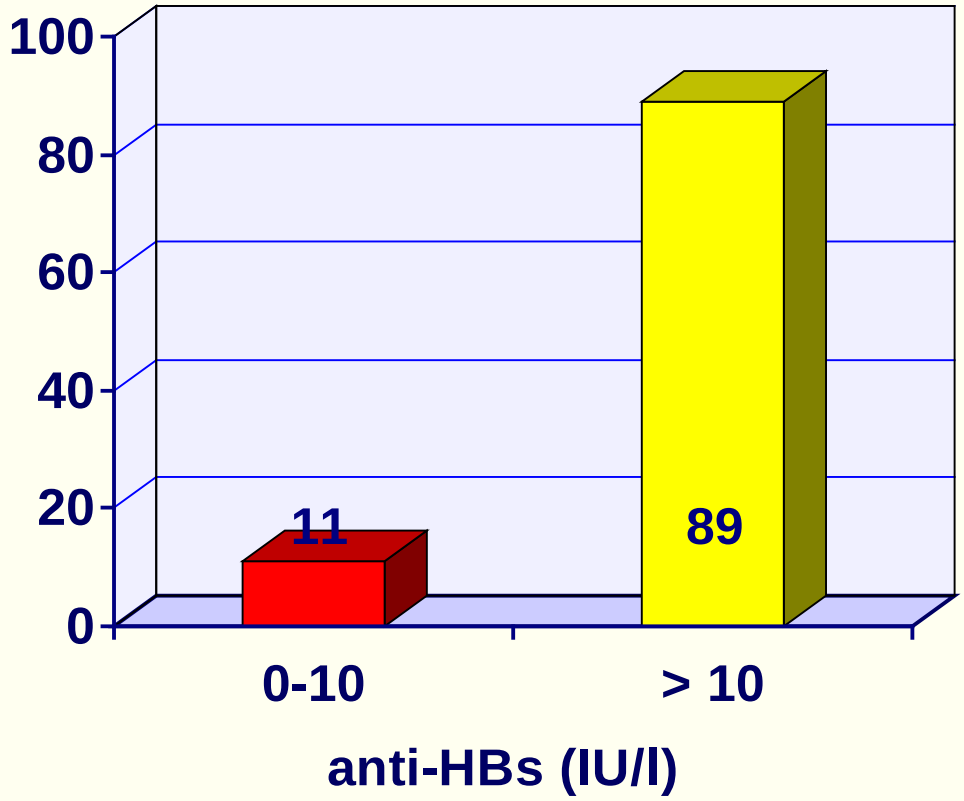
Gottlieb et al, Am J Epidem 1967;85:207-219 (Diphtherie)
Gesemann et al, Vaccine 1995; 13: 443-447 (Hepatitis B)
Van Herck et al, J Med Virol 2001; 63:1-7 (Hepatitis A)

Anti-HBs 10 yrs after hep B vaccination
in children and young adults in Italy

children (n=1212)
vaccinated as newborns

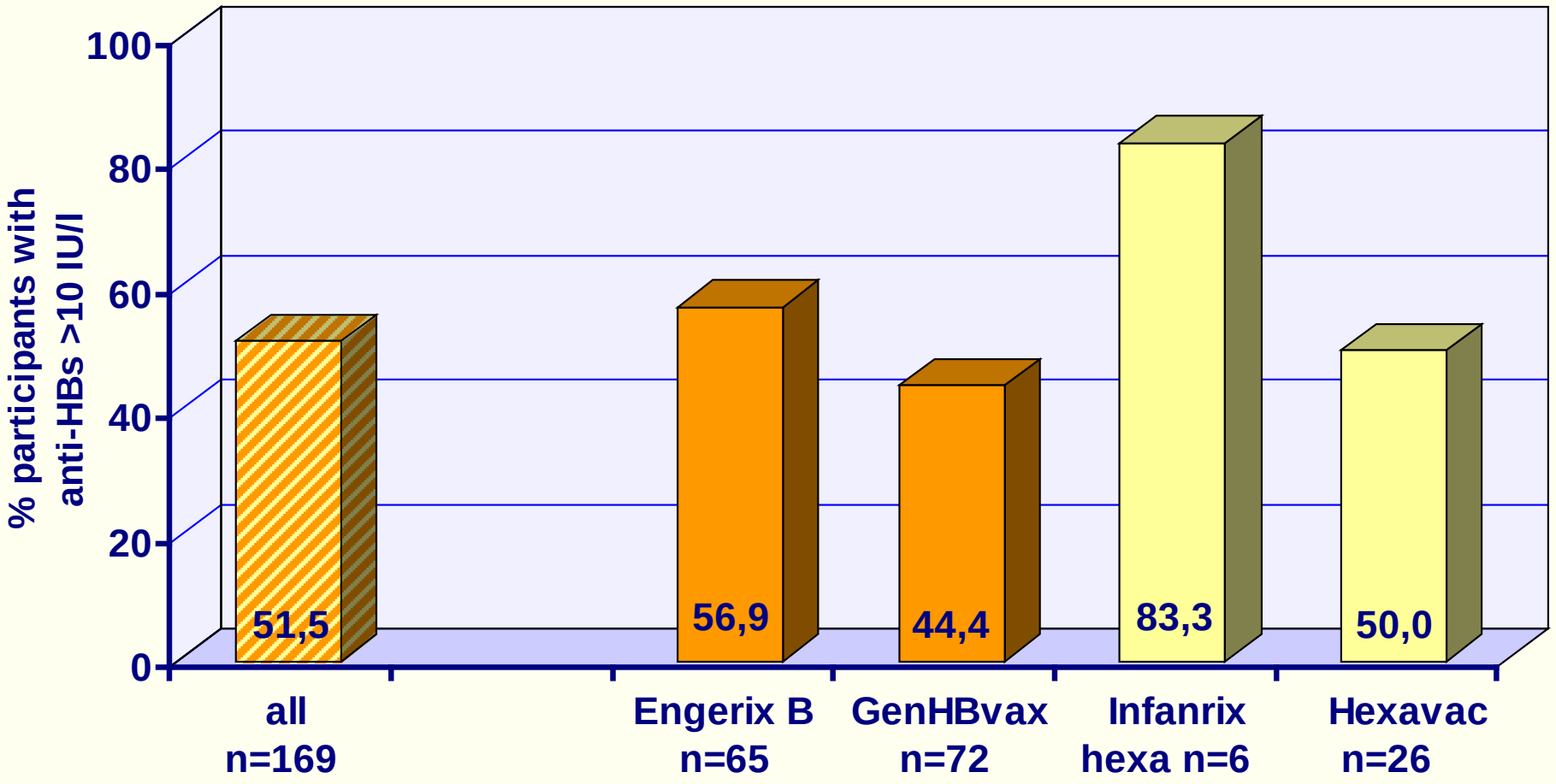


recruits (n=446)
vaccinated with 12 years



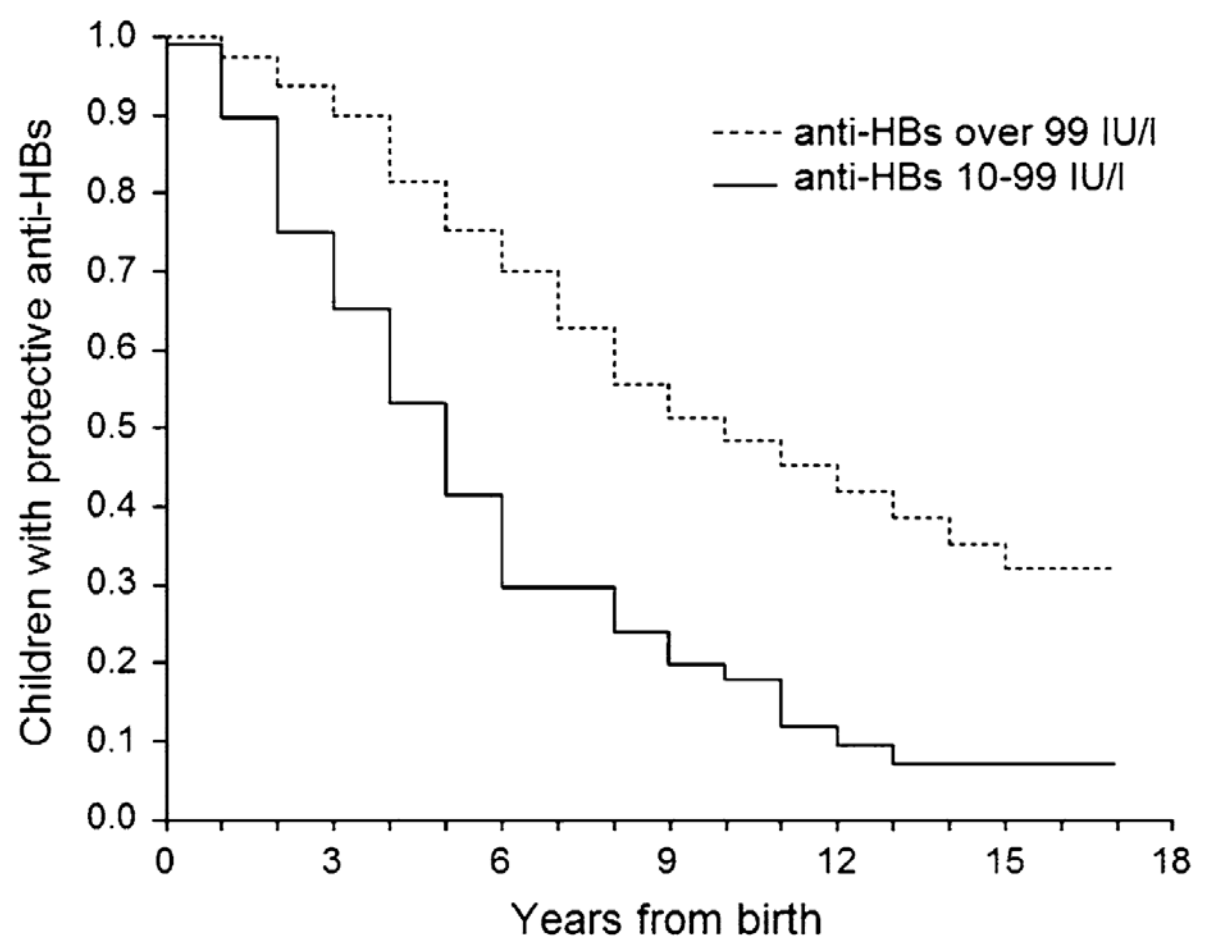
Zanetti et al Lancet 2005; 366: 1379-1384

Anti-HBs 8-12 yrs after hep B vaccin.
with different vaccines in children/adolescents in Bavaria



Huber, Wenzel et al unpublished

Waning of anti-HBs according to anti-HBs after vaccination at birth



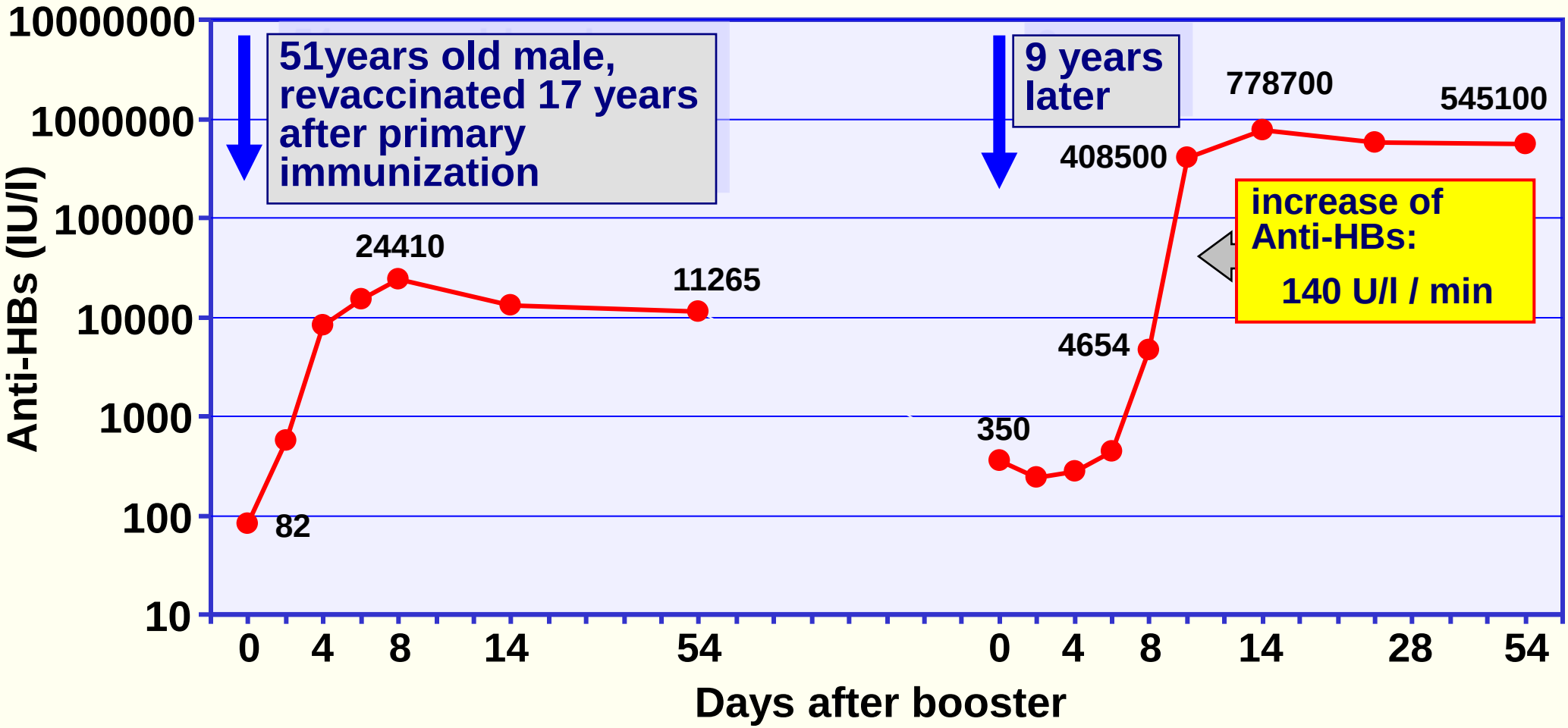
Roznovsky et al Infection 2010;38:395-400

Persistence of Anti-HBs

- persistence of anti-HBs is a function of ***peak anti-HBs-level*** and ***time after vaccination***
- peak anti-HBs level depends mainly on age at vaccination, vaccine and vaccine dosage and genetic factors (in immunocompetent individuals)
- after 20 years, only about 20-30% of individuals vaccinated as newborns are still anti-HBs-positive with values ≥10 IU/l

Vaccination against Hepatitis B:

What is an anamnestic reaction? An example

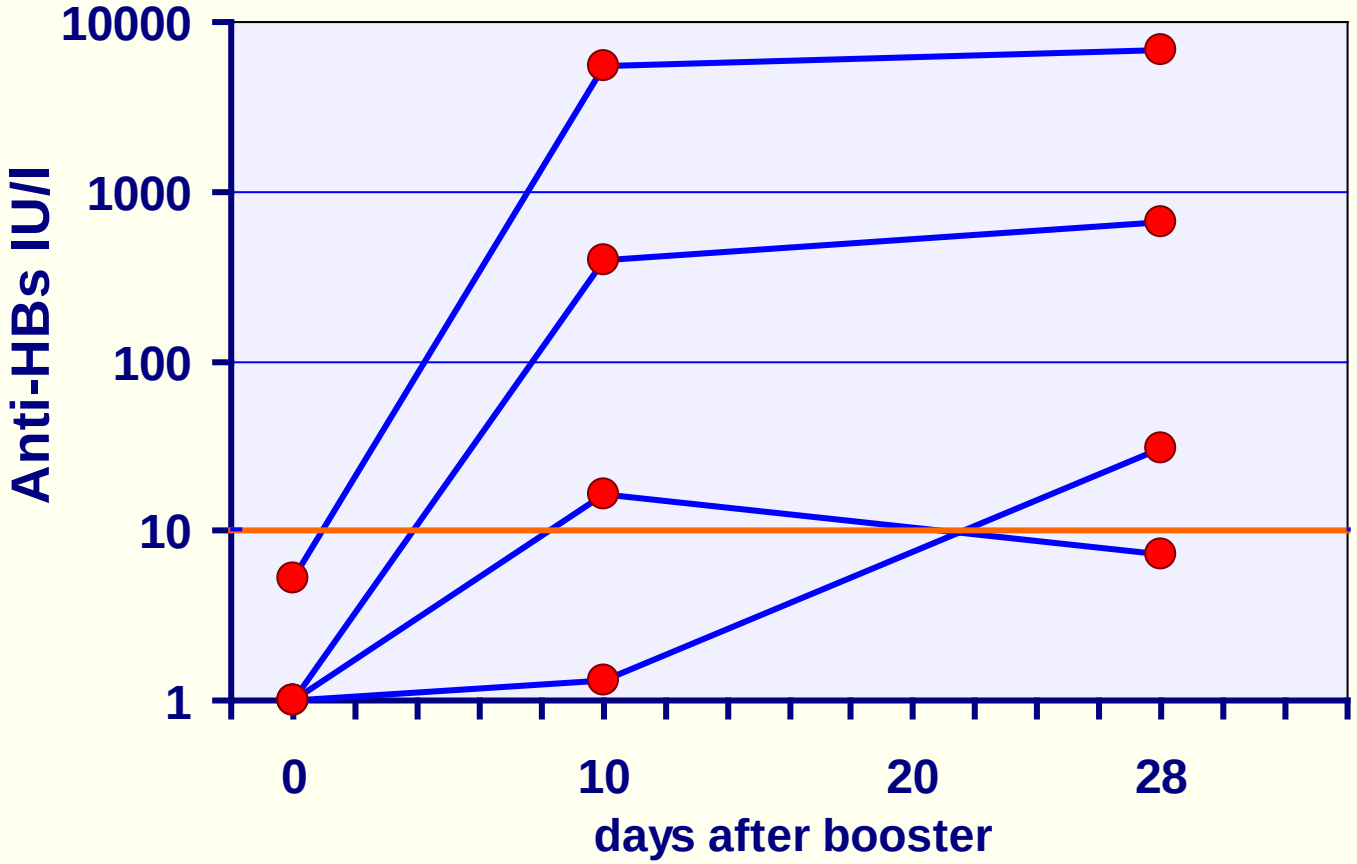


Vaccination against Hepatitis B:
criteria for an “anamnestic response”

- **in anti-HBs-positive individuals (anti-HBs ≥ 10 IU/l):**
  - ***4fold increase of anti-HBs within 4 weeks***
- **in individuals with anti-HBs < 10 IU/l („anti-HBs-negative“):**
  - ***increase of anti-HBs to ≥ 10 IU/l after 10-14 days and/or 28 days***

Vaccination against Hepatitis B:

What is an anamnestic reaction?



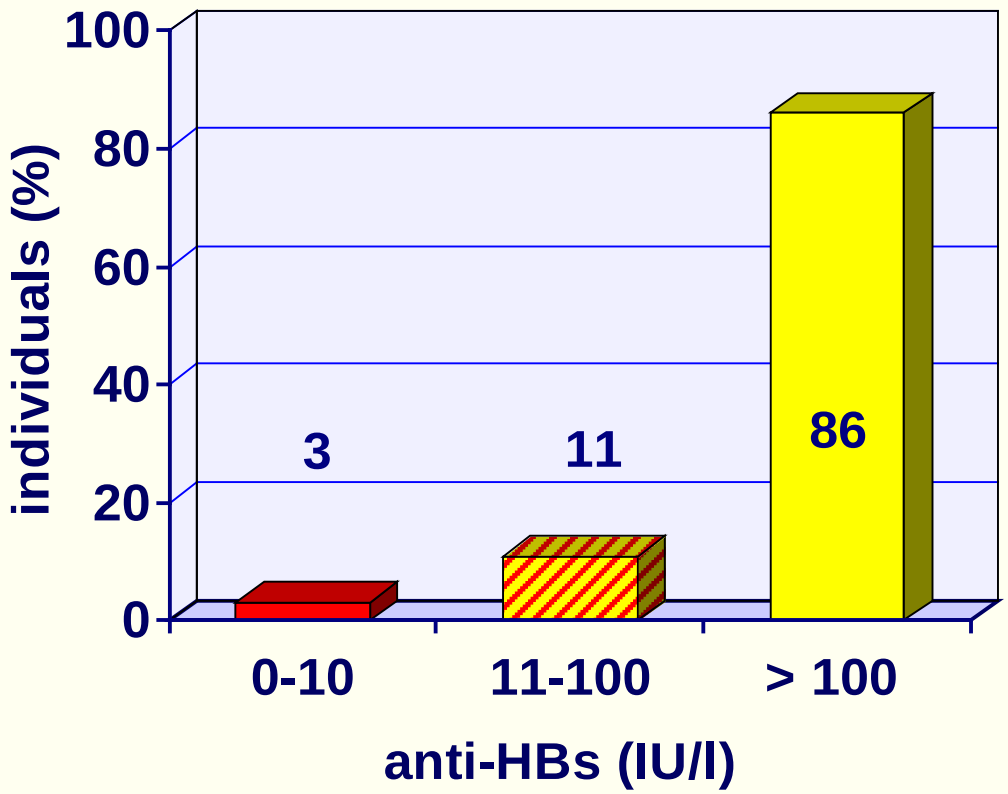
4 children were revaccinated 8-12 years after primary immunization. All showed anti-HBs below 10 IU/l before booster.

Huber, Wenzel et al unpublished

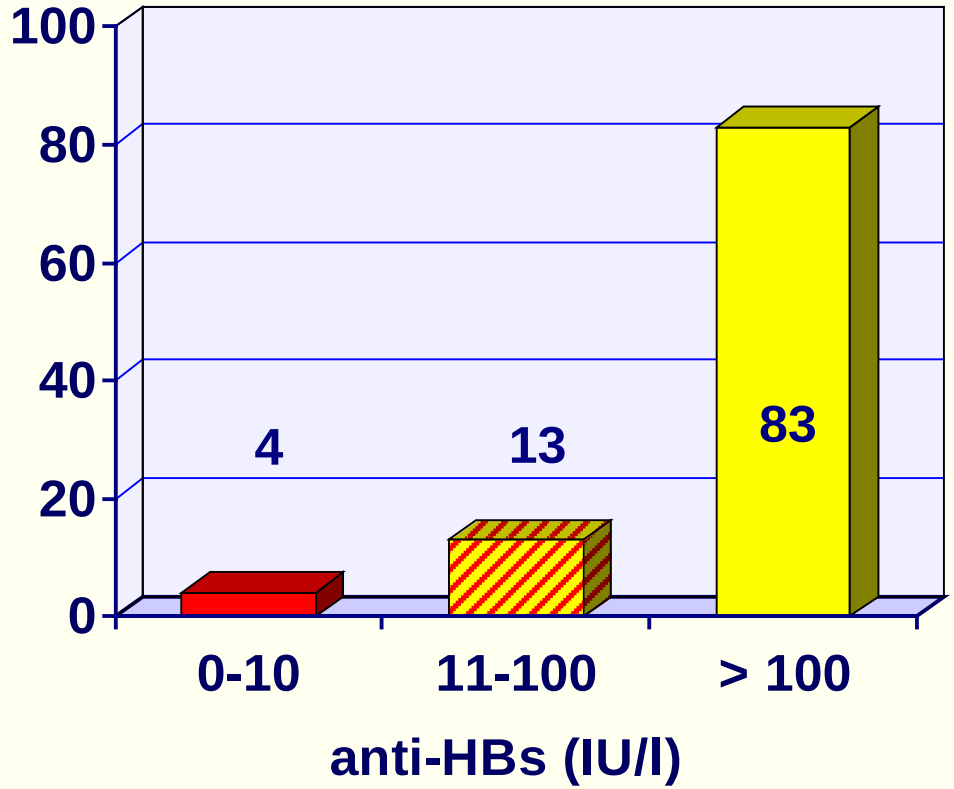
Revaccination of individuals <10 IU/l

10 years after basic course of immunisation

children (n=342)
vaccinated as infants



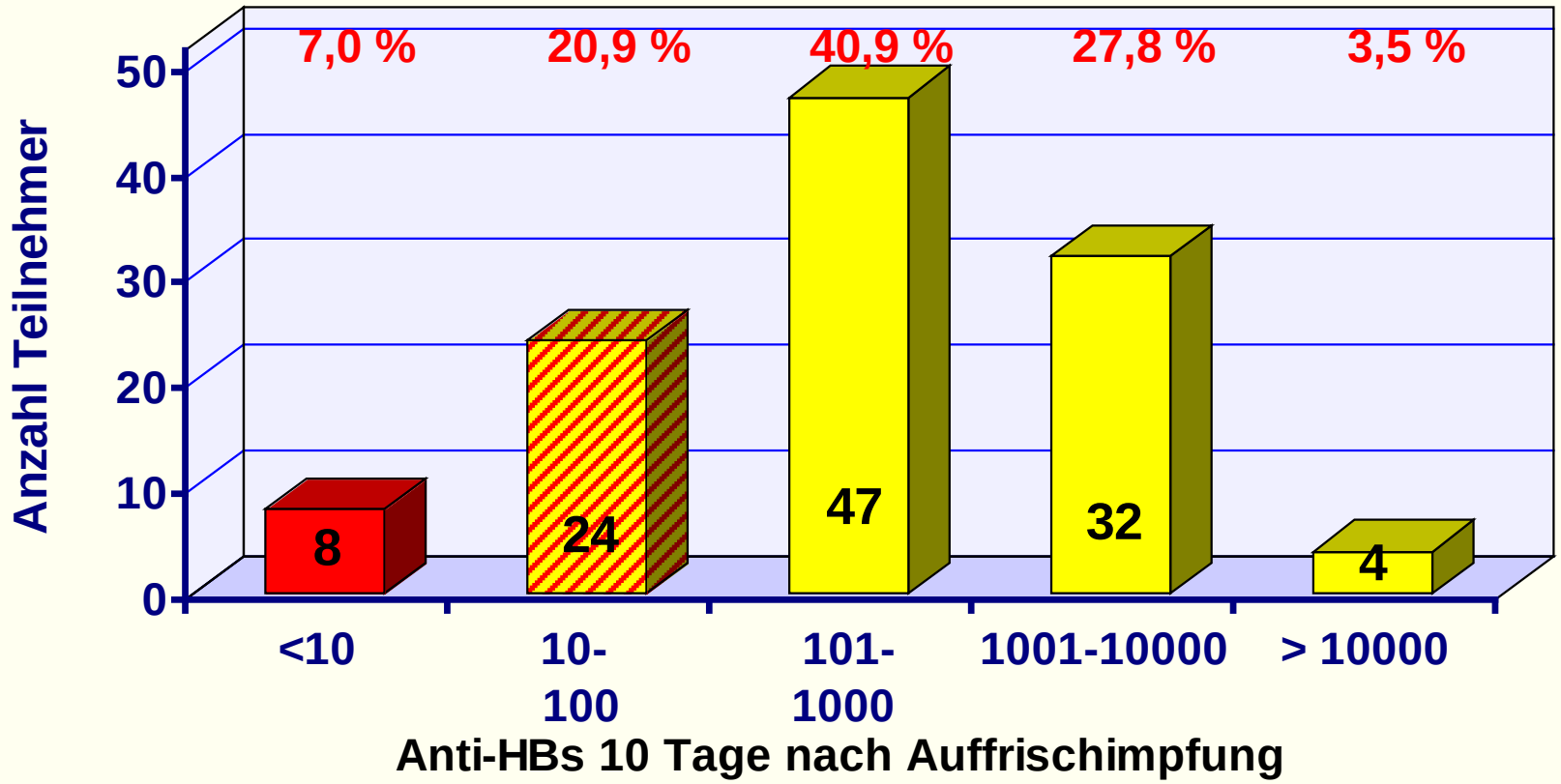
recruits (n=48)
vaccinated with 12 years



Zanetti et al Lancet 2005; 366: 1379-1384

Revaccination of individuals <10 IU/l

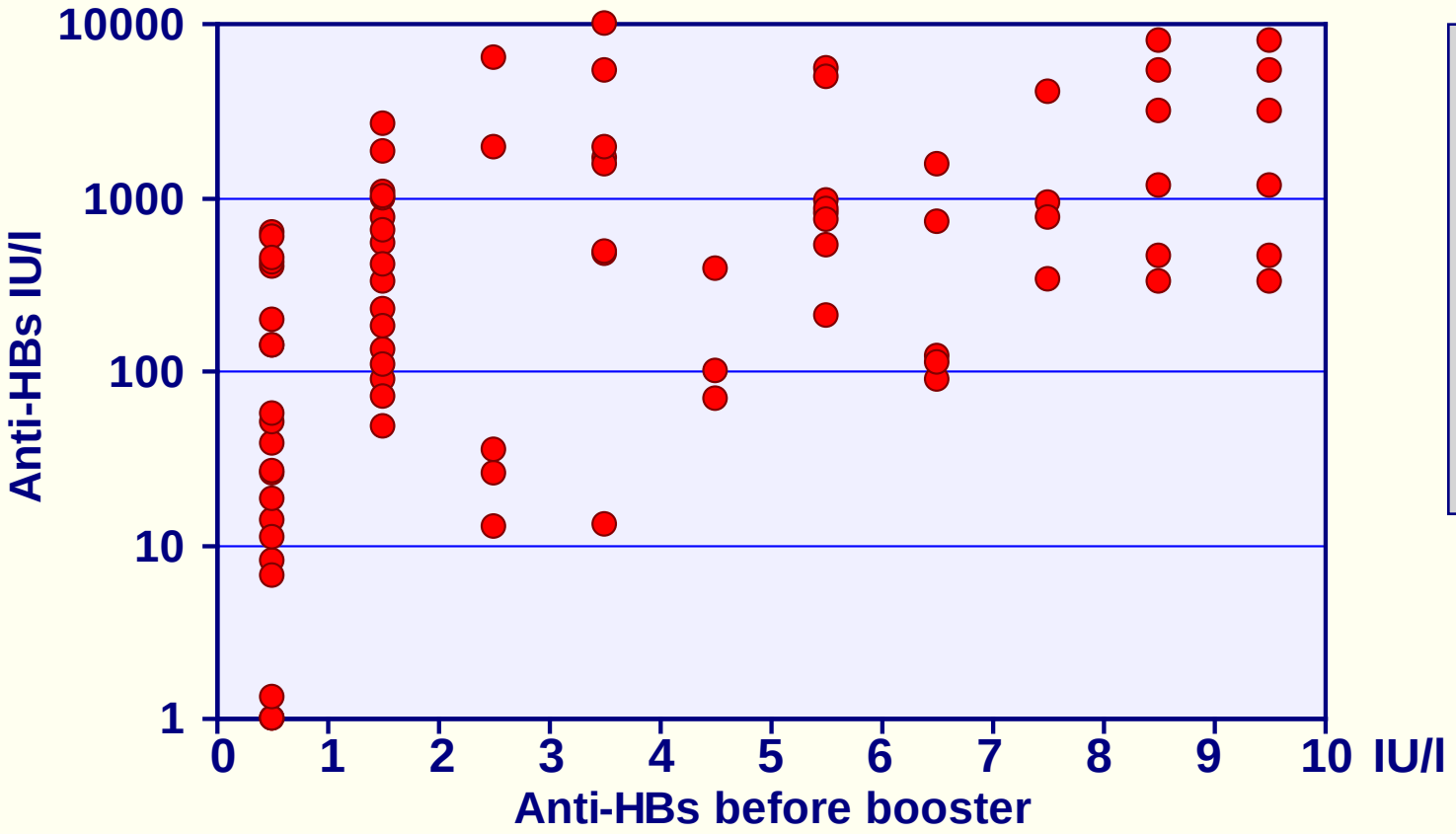
8-12 years after basic course of immunization/Bavaria



Huber, Wenzel et al unpublished

Anti-HBs after revaccination

according to Anti-HBs-concentration before booster



82 children were revaccinated 8-12 years after primary immunization. All showed anti-HBs below 10 IU/l before booster.

Huber, Wenzel et al unpublished

Anamnestic response to revaccination
15 - 24 years after hepatitis B vaccination in newborns

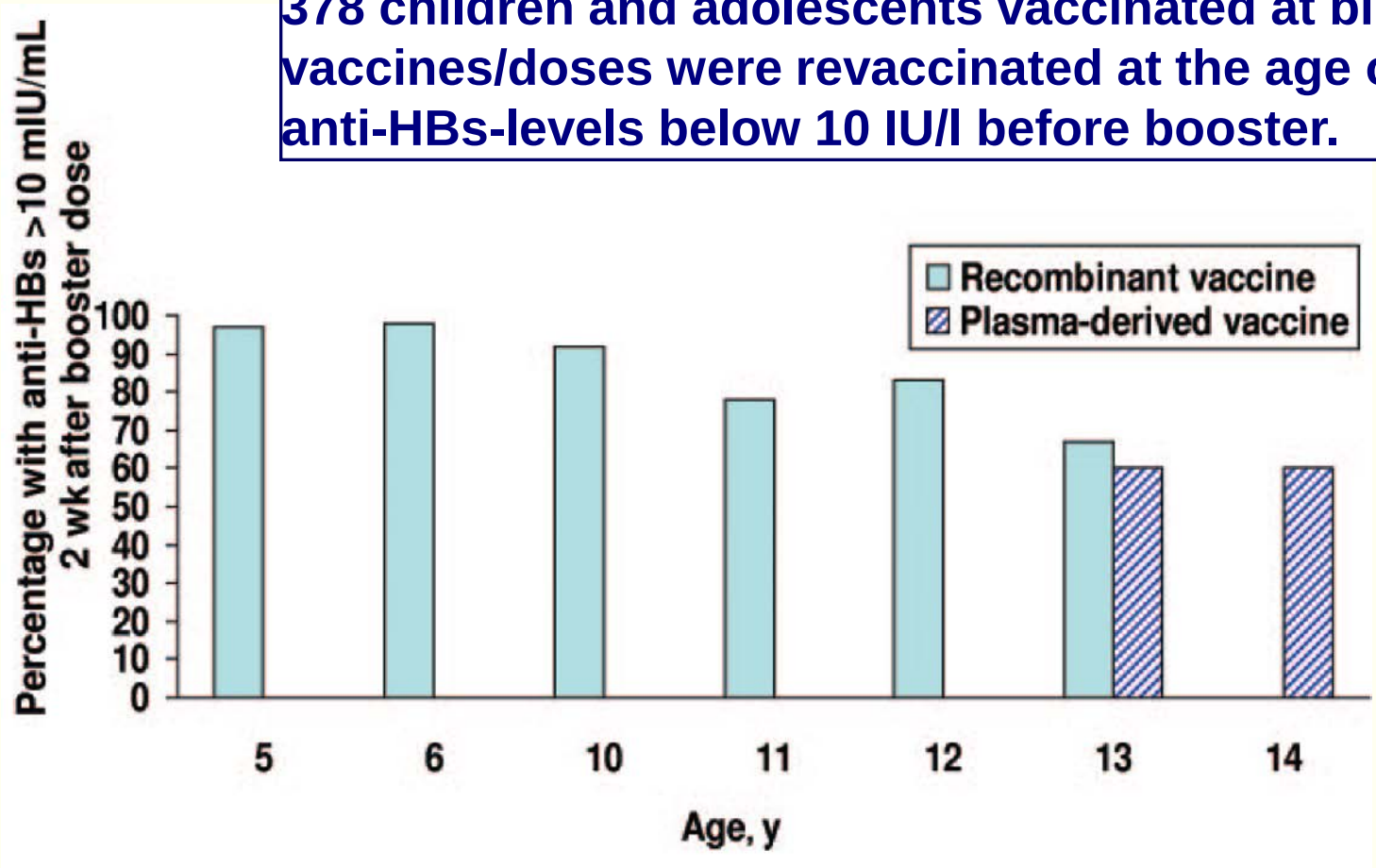
Population	vaccine (µg HBsAg)	follow up years	anti-HBs ≥10 IU/l (%)	response to booster n/n	response to booster %
Micronesian[1] (n=105)	recombinant 5 / 2.5 / 2.5	18	7	39/ 90	43%*
Chinese[2] (n=5981)	plasma 4x10(Pasteur)	15-18	37	393/551	71%**
Chinese[3] (n=127)	plasma 4x10(Pasteur)	18-23	-	26-96/127	21-76%*,**
Chinese[4] (n=404)	plasma 3x5 (Merck)	24	30	45-55/ 63[#] 23-32/ 40[##]	71-87%*,** 58-80%*,**

* % at day 10-14 ** % at day 28 [#] anti-HBs+ at year 5 [##] anti-HBs- at year 5

[1] Bialek et al, Pediatr Infect Dis J 2008;27:881; [2] Lu et al, J Infect Dis 2008;197: 1419;
[3] Jan et al, Hepatology 2010;27:881; [4] Zhu et al Vaccine 2011;29:7835

Anamnestic response in children / adolescents vaccinated at birth

378 children and adolescents vaccinated at birth with different vaccines/doses were revaccinated at the age of 5-14 years. 292 had anti-HBs-levels below 10 IU/l before booster.



Samandari et al, Pediatrics 2007;120:e373-81

Persistence of „boostability“

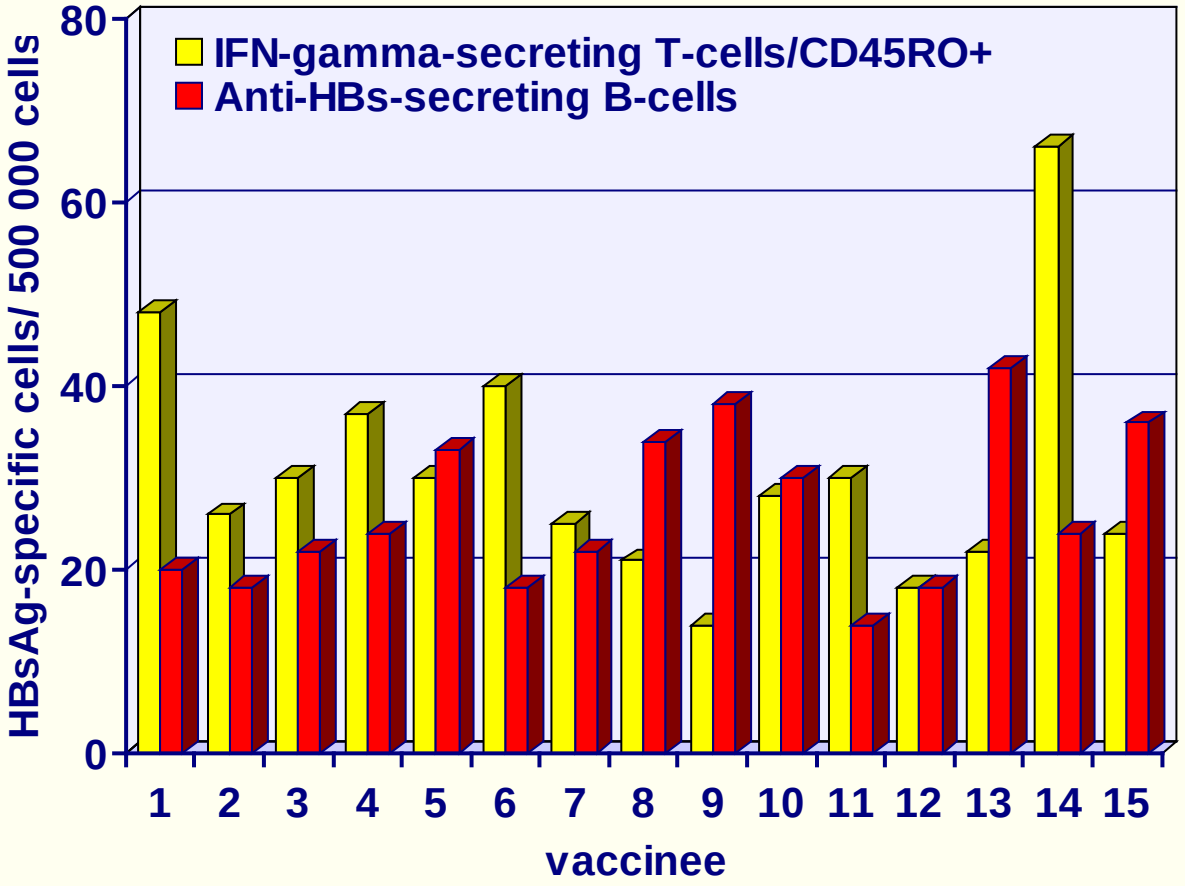
- boostability shows the presence of immune memory
- it outlasts the presence of anti-HBs
- it can be demonstrated in the vast majority of vaccinees for at least 10 years
- loss of “boostability” shown in recent reports indicates that immune memory may wane with time
- waning immune memory seems to be more frequent in individuals vaccinated at birth and/or with low doses of vaccine

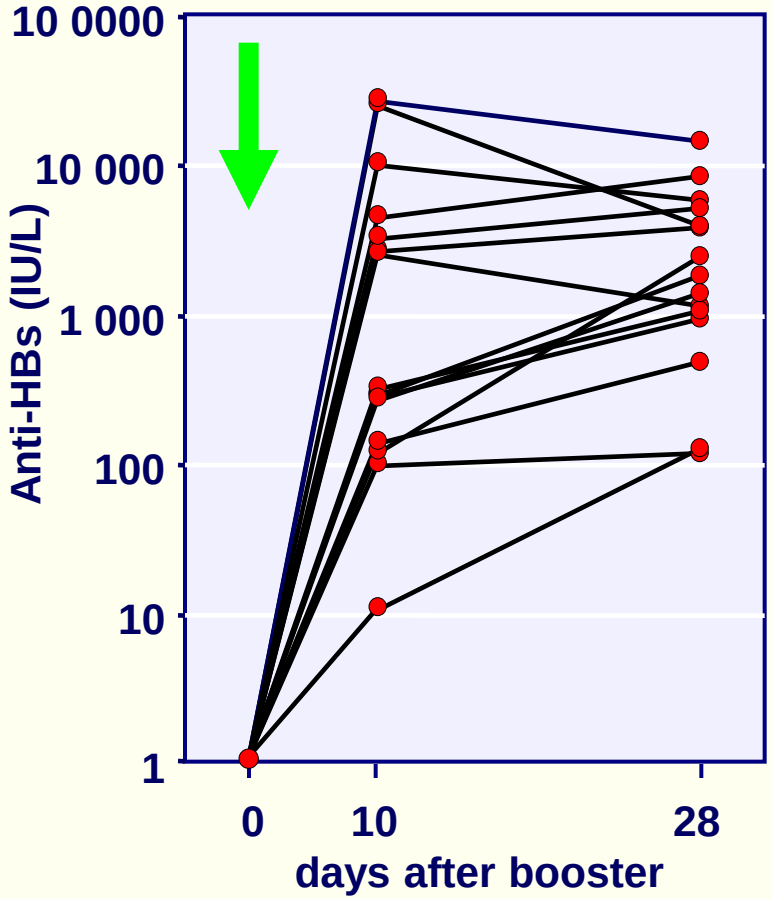
Demonstration of HBsAg-specific memory T- and B- cells

- **demonstration of *HBsAg-specific T-cells***
  - **proliferation assays**
  - **cytokine secreting cells (ELI-spot)**
  - **intracellular cytokines (FACS-analysis)**
- **demonstration of *anti-HBs-secreting B-cells* in vitro (ELI-spot)**

Demonstration of memory T-and B-cells

in 15 vaccinated individuals after loss of anti-HBs

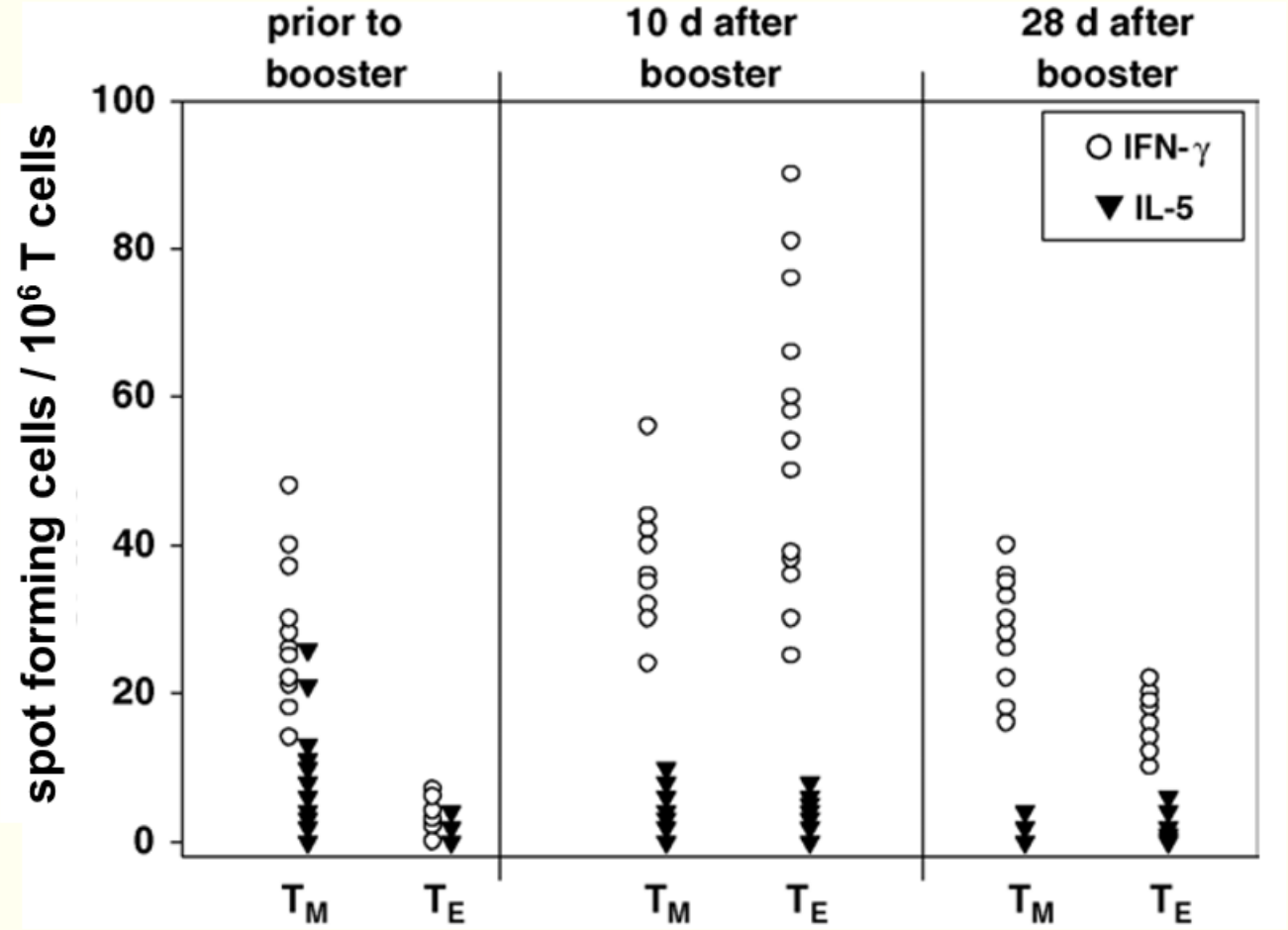




Bauer, Jilg, Vaccine 2006;24:572-7

HBsAg-specific T-memory/-effector cells

before and after booster vaccination



T_M: memory T cells
CD4+/CD45R0+

T_E: effector T cells
CD4+/CD45RA+

Bauer, Jilg, Vaccine 2006;24:572-7

T-cell memory

IFNγ / IL2 secreting cells before /after booster vaccination

Response category	IFN-γ		IL-5	
	Before booster	After booster	Before booster	After booster
<1 SFCs/10^6 PBMCs	76 (82.6)	63 (68.5)	87 (94.6)	41 (44.6)
>1–5 SFCs/10^6 PBMCs	16 (17.4)	13 (14.1)	5 (5.4)	31 (33.7)
>5–10 SFCs/10^6 PBMCs	0	9 (9.8)	0	10 (10.9)
>10–100 SFCs/10^6 PBMCs	0	5 (5.4)	0	7 (7.6)
>100 SFCs/10^6 PBMCs	0	2 (2.2)	0	3 (3.3)

NOTE. Data are no. (%) of subjects.

Lu et al J Infect Dis 2008;197:1419-26

Demonstration of HBsAg-specific memory T- and B- cells

- important research method, but at present not very well suited for the determination of the duration of immune memory, as the tests are
  - technically demanding, tedious and expensive
  - influenced by the need of not standardized biological reagents as HBsAg, peptides, human sera, therefore results from different laboratories hardly comparable
  - difficult to interprete, as only 5-8% of lymphocytes in the peripheral blood
- determination of „boostability“ probably more sensitive!

Summary and conclusion I
How long does memory last?

- presence of anti-HBs depends on maximal value after primary course of vaccination – in individuals vaccinated in infancy, after 10 years 50-60%, after 20 years only 20-30% still positive (more when vaccinated as adolescents?)

- ability to mount an anamnestic response („boostability“) outlasts presence of anti-HBs, will be maintained for at least 10 years in vast majority of vaccinees. Waning of boostability with time seen especially in individuals with low initial anti-HBs-titers

Summary and conclusion II
Are boosters needed?

- at least in individuals vaccinated in infancy booster doeses might be considered for individual protection

- in this case, booster doses should be given as long as memory is present, i.e. after 10-15 years (e.g. in 12-14 years old, before risk of sexual transmission starts)