Viral Hepatitis Prevention Board Meeting

Sevilla, Spain, March 11-12, 2004

Hepatitis B vaccine: long-term efficacy, booster policy, and impact of HBV mutants on hepatitis B vaccination programmes

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Immune memory after hepatitis B vaccination

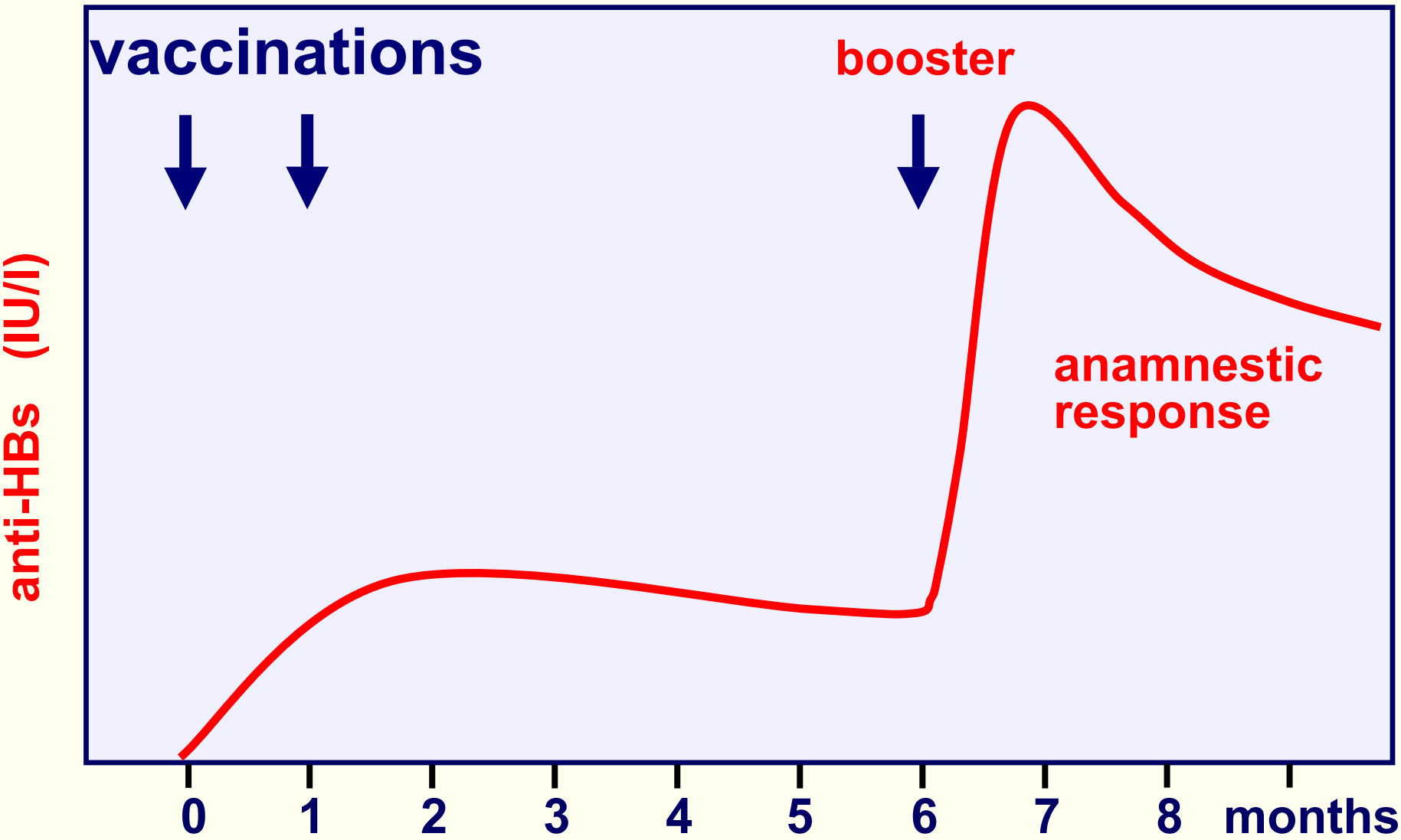
Wolfgang Jilg
Institute for Medical Microbiology and Hygiene
University of Regensburg

what is memory?

immunologic memory

- **cardinal feature of the *adaptive* immune system**
- **ability to respond *again* to an antigen with a *more rapid, larger and qualitatively different* response *(anamnestic response)***

production of anti-HBs during Hep B vaccination



immunologic memory
role for hepatitis B immunisation

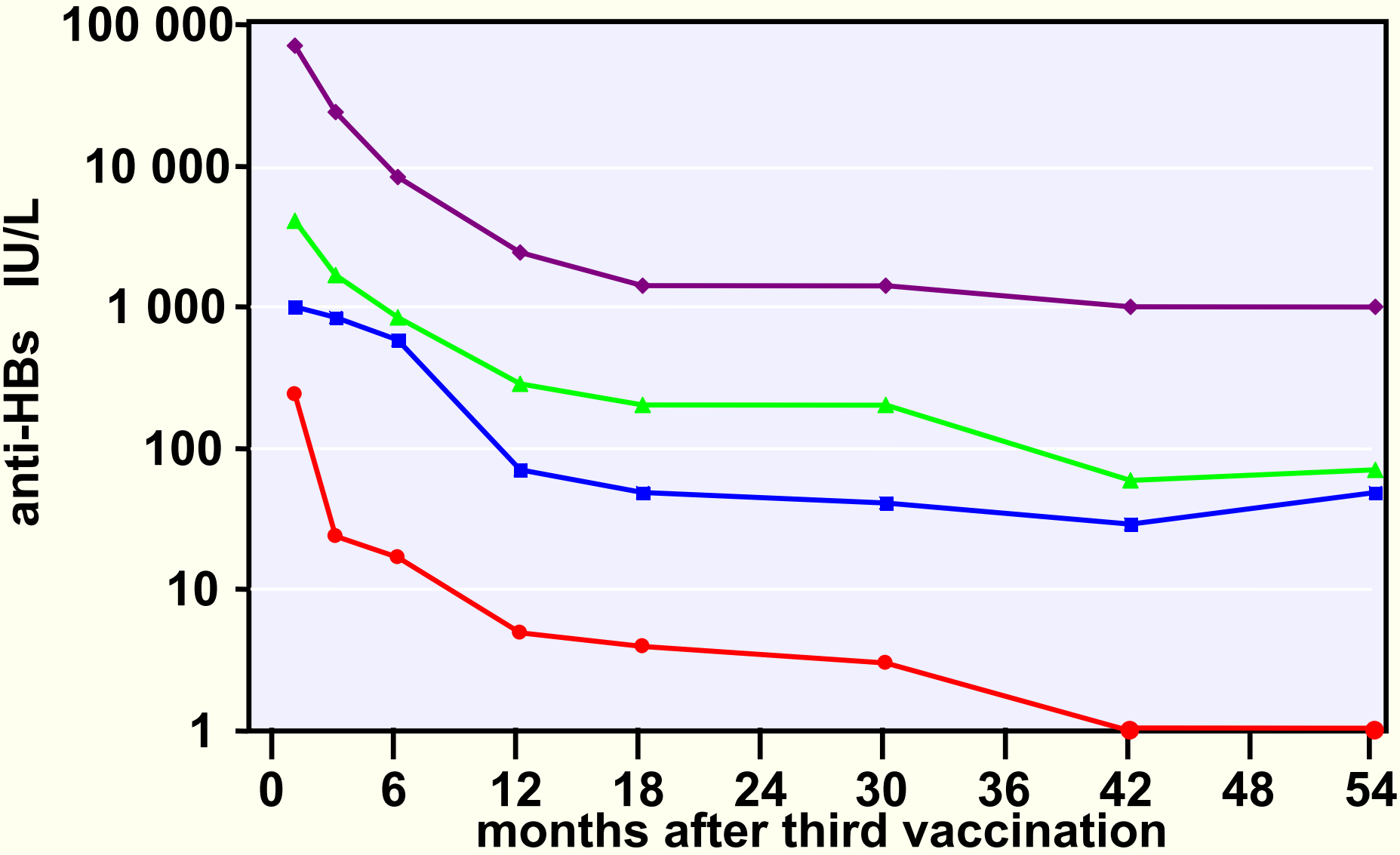
- responsible for height and persistence of anti-HBs after third (booster) dose
- protects against disease after loss of anti-HBs in successfully vaccinated individuals
- may play a role for protection against antibody-escape mutants (as long as T-cell epitopes are not involved)

persistence of anti-HBs

protection after Hep B vaccination

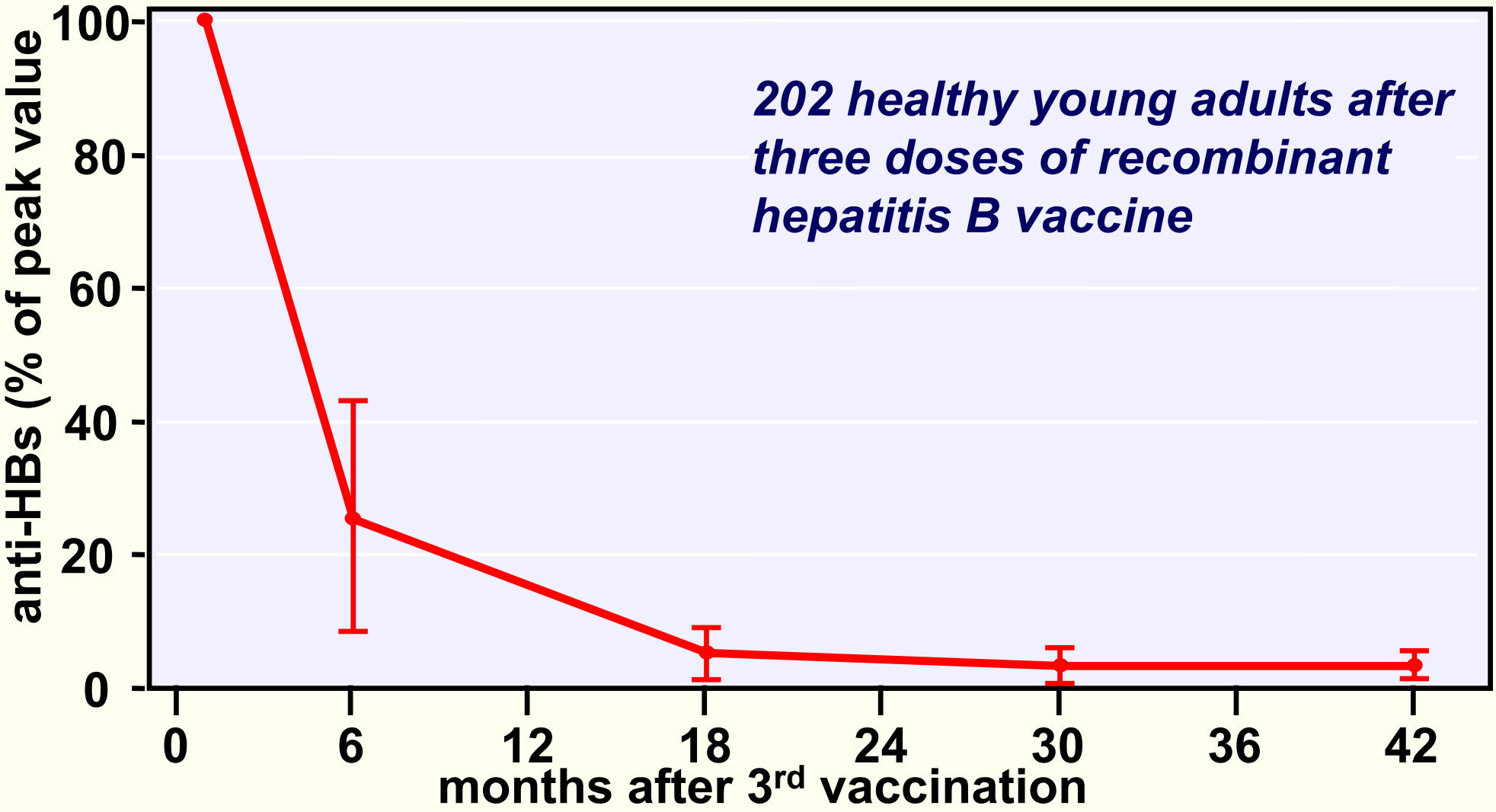
- ***protection against infection*** **bound to anti-HBs-concentrations ≥10 IU/l**
  persistence depends on initial (peak) anti-HBs concentration

decrease of anti-HBs in 4 individuals after 3rd dose



Jilg et al, Lancet 1990; 335:173

percentage decrease of anti-HBs



Jilg et al, Infection 1989;17:70

kinetics of anti-HBs after hepatitis B vaccination

- very similar in every vaccinee *irrespective of the peak antibody level after the third vaccination*
- half-life of anti-HBs is *function of time*, being *very short initially* and *becoming longer with time* after last vaccination
- influenced by *disturbances to the immune system*, specific disorders (e.g. Down-Syndrome), certain drugs (e.g. antiepileptics)

Jilg et al, J Hepatol 1988;6:201; Coursaget et al, Lancet 1991;337:1180; Gesemann et al, Vaccine 1995;13:443; Vellinga et al, J Med Virol 1999; 57:100

how long does anti-HBs persist?

persistence of anti-HBs after hep.B vaccination

Population	time after first vacc.	anti-HBs ≥10 IU/l (%)
Alaskan natives (n=959) *Wainwright et al 1997*	10 yrs	76
Taiwanese children (n=539) *Wu et al 1999*	10 yrs	85
Italian children (n=223) *Mele et al 1999*	11-14 yrs	75
Chinese children (n=52) *Liao et al 1999*	15 yrs	50

in 10 - 50% of all succesfully vaccinated individuals the anti-HBs concentration decreases below 10 IU/l within 10 years

as protection against infection is bound to anti HBs concentrations above 10 IU/l these individuals are again susceptible to infection

break-through infections

10-year follow-up after Hep B vaccination in high-risk infants

972 Taiwanese children of HBsAg-positive mothers

➔ **HBIG at birth + vaccine at month 0,1, 6**

4 different doses of plasma-derived vaccine tested (2.5 / 5 / 10 / 20 µg)

month 12:

805 children anti-HBs pos., HBsAg and anti-HBc neg.

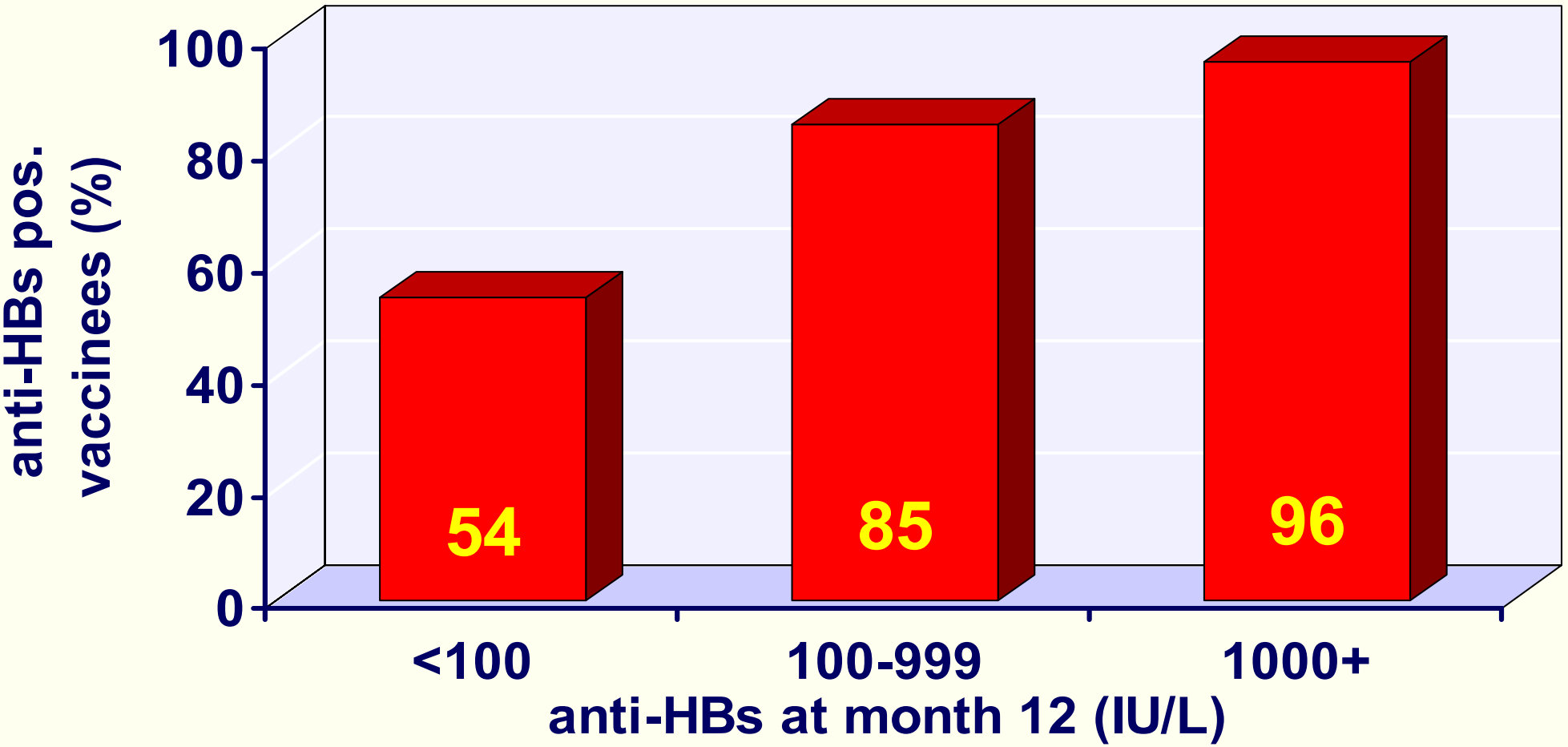
after 10 years:

539 available for analysis

Wu et al JID 1999; 179: 1319

anti-HBs 10 years after HB vaccination

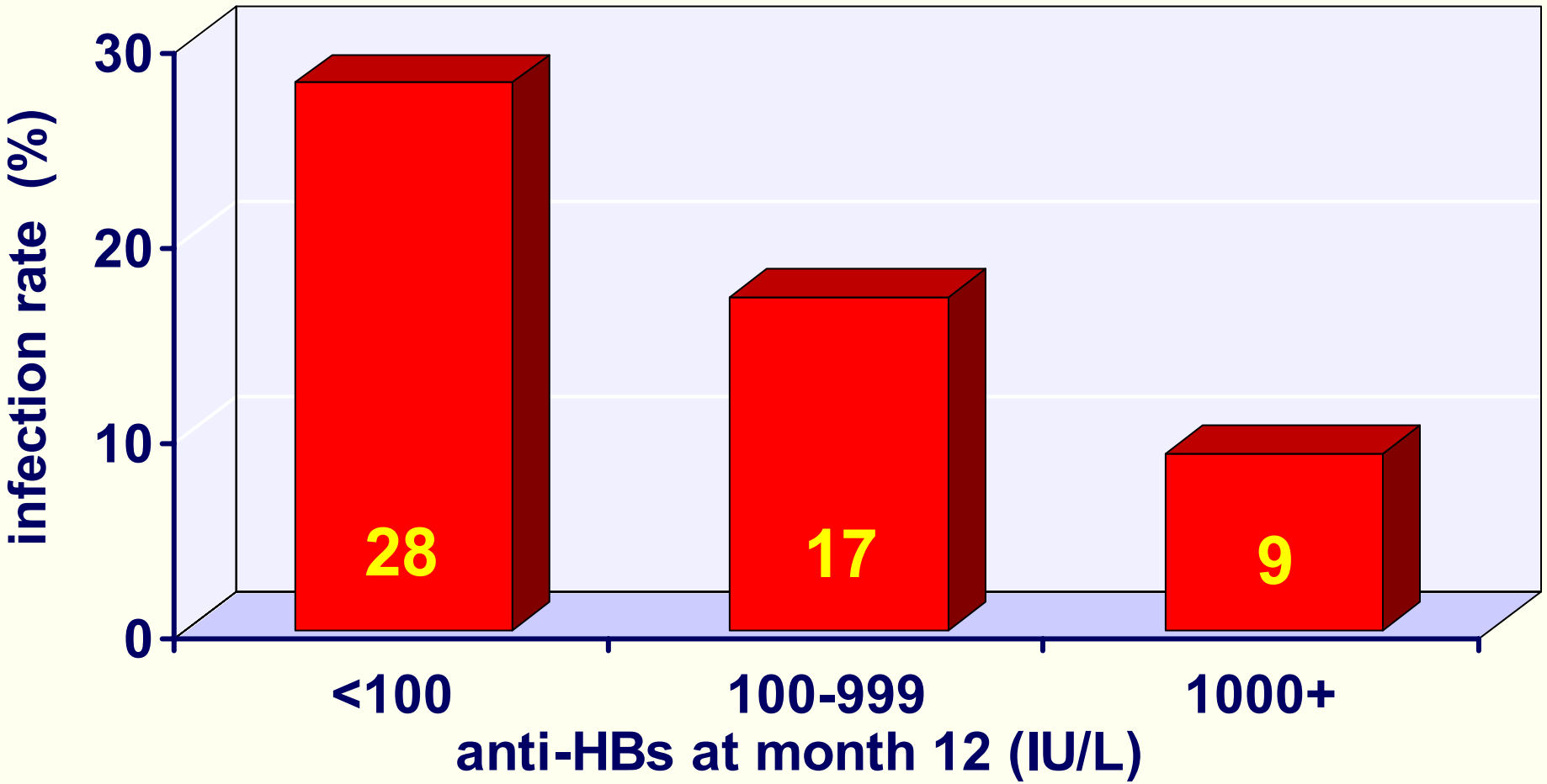
according to anti-HBs level at 12 months (Wu et al 1999)



Wu et al JID 1999; 179: 1319

infection rate 10 yrs after HB-vaccination

according to anti-HBs level at 12 months (Wu et al 1999)



Wu et al JID 1999; 179: 1319

break-through infections in successfully vaccinated individuals

population	time after 1st vaccination	n (%) positive for anti-HBc	HBsAg
homosex. men (n=634) *Hadler et al 1991*	7-9 yrs	46 *(7)**	2 *(0.3)***
eskimos in Alasca (n=1630) *Wainwright et al 1997*	10 yrs	13 *(0.8)**	0
children in Taiwan (n=805) *Wu et al 1999*	10 yrs	109 *(14)**	4 *(0.5)*
children in Gambia (n=731) *Whittle et al 2002*	14 yrs	79 *(11)**	2 *(0.3)*

** clinically silent* *** HIV-positive*

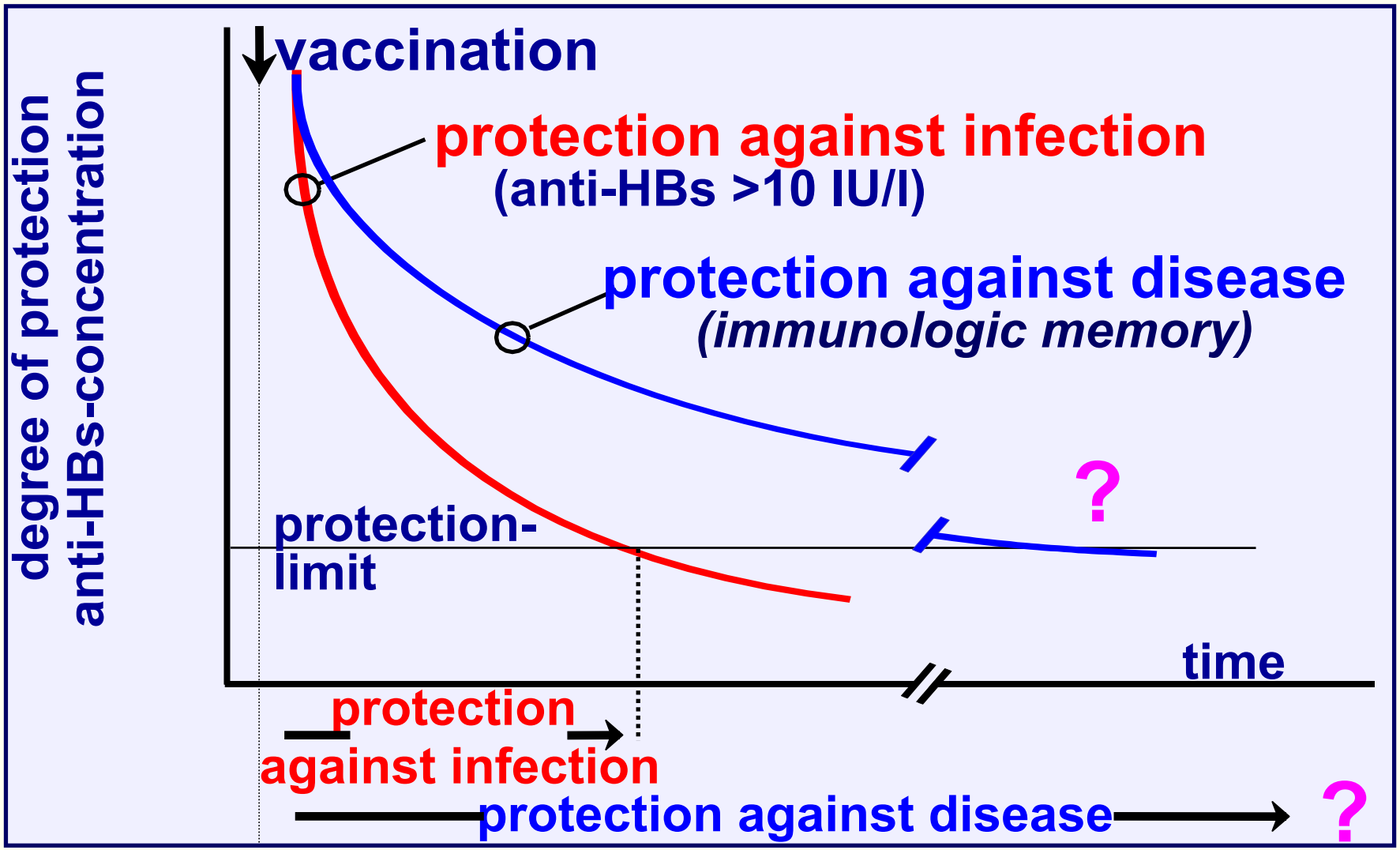
break-through infections after successful Hep B vaccination

- risk of hepatitis B infection is *inversely related to the maximal antibody response* to vaccine
- risk of infection *increases with declining anti-HBs*
- vast majority of infections in successfully vaccinated individuals are *clinically silent*
- protection against clinically important disease *outlasts the presence of detectable antibodies*

Hadler et al, NEJM 1986; 315: 209;
Wu et al JID 1999; 179: 1319

Wainwright et al, JID 1997; 175: 674;
Whittle et al BMJ 2002; 325: 569

protection after Hep B vaccination



protection against disease due to presence of immunologic memory

- vaccination induces *B- and T-memory cells*

  → rapid proliferation after contact with antigen, production of cytokines and specific antibodies *(„anamnestic response“)*

- in case of infection the anamnestic response prevents its further spread, downregulates viral replication and finally eliminates the virus

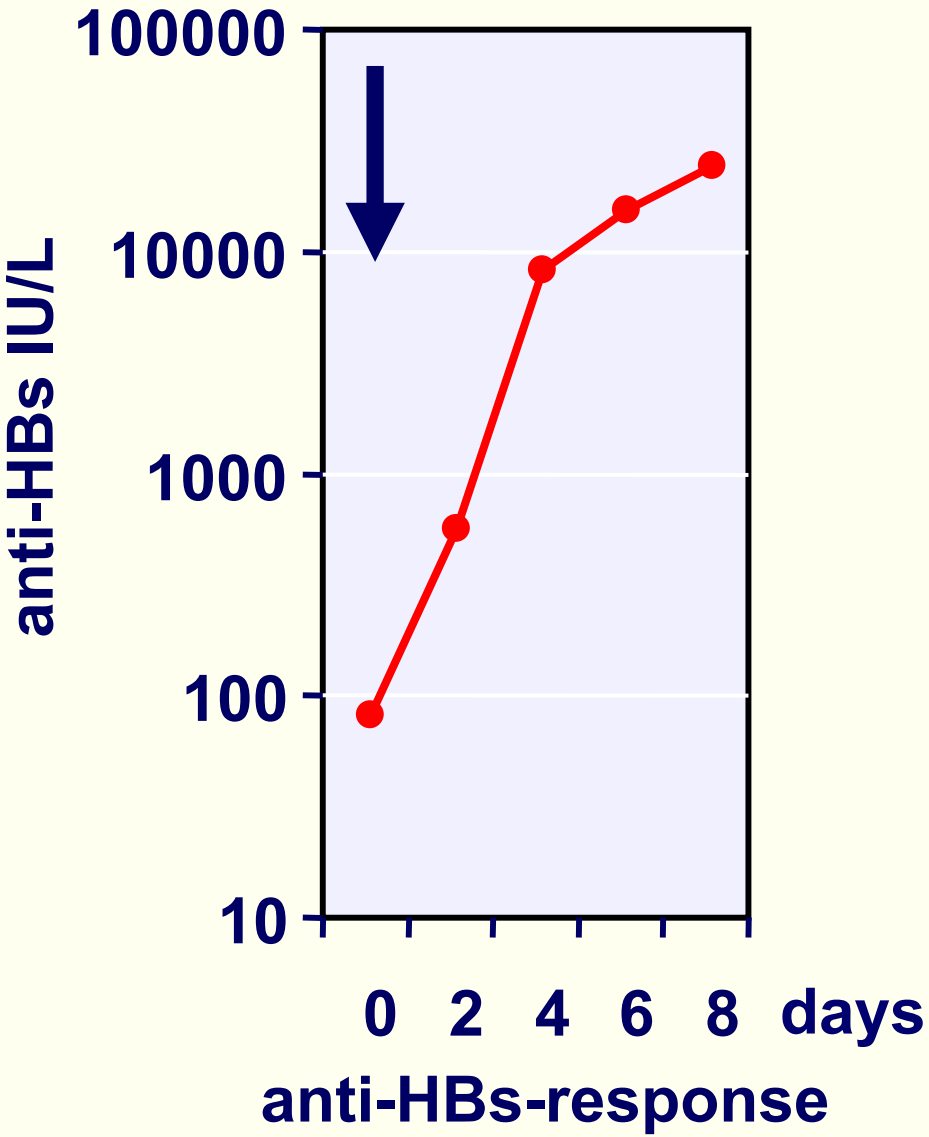
  → *prevents disease and chronic infection*

how can we prove the presence of an immunologic memory ?

methods to demonstrate immunologic memory after hepatitis B vaccination

- ***anamnestic anti-HBs response*** **after revaccination**

anamnestic response 17 years after HepB vacc.



within 8 days anti-HBs increases from 80 IU/l to 25 000 IU/l

>300 fold increase in anti-HBs

mean increase of 130 IU per hour or 2 IU per min

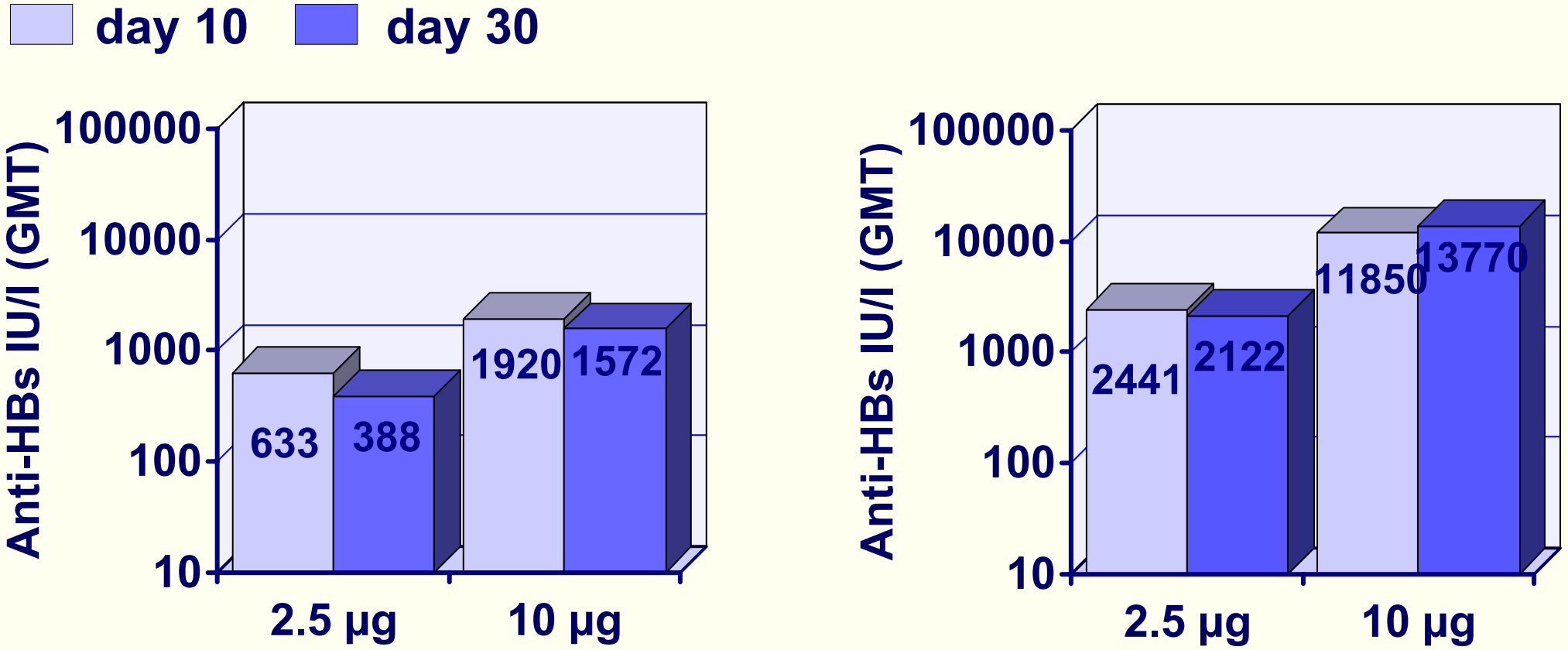
anamnestic response to revaccination of 203 individuals ≥10 years after first Hep B-vaccination

group	time after first vaccination	anamnestic reponse at (%)
ital. children (n =147*) *Da Villa et al 1996*	10 years	96
ital. children (n =17*) *Resti et al 1997*	10 years	100
US children (n =14) *West et al 1994*	12 years	100
US children/adults (n =25**) *Watson et al 2001*	13 years	100

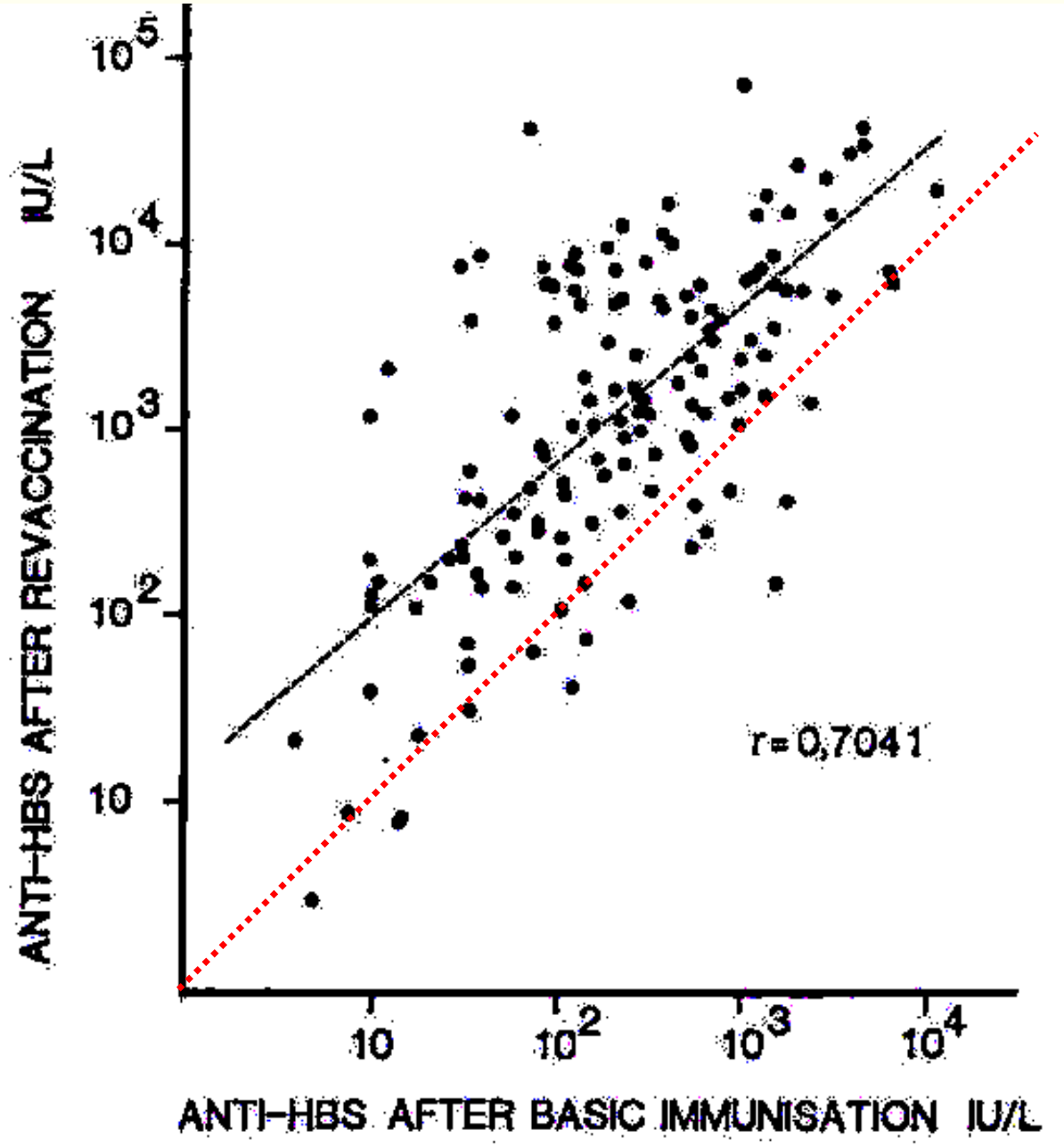
** all anti-HBs neg.* *** 5 anti-HBs neg.*

anamnestic response to booster doses

with 2.5 or 10 µg HBsAg in previously immunized HCW (n=59)



Williams et al Vaccine 2001;19:4081

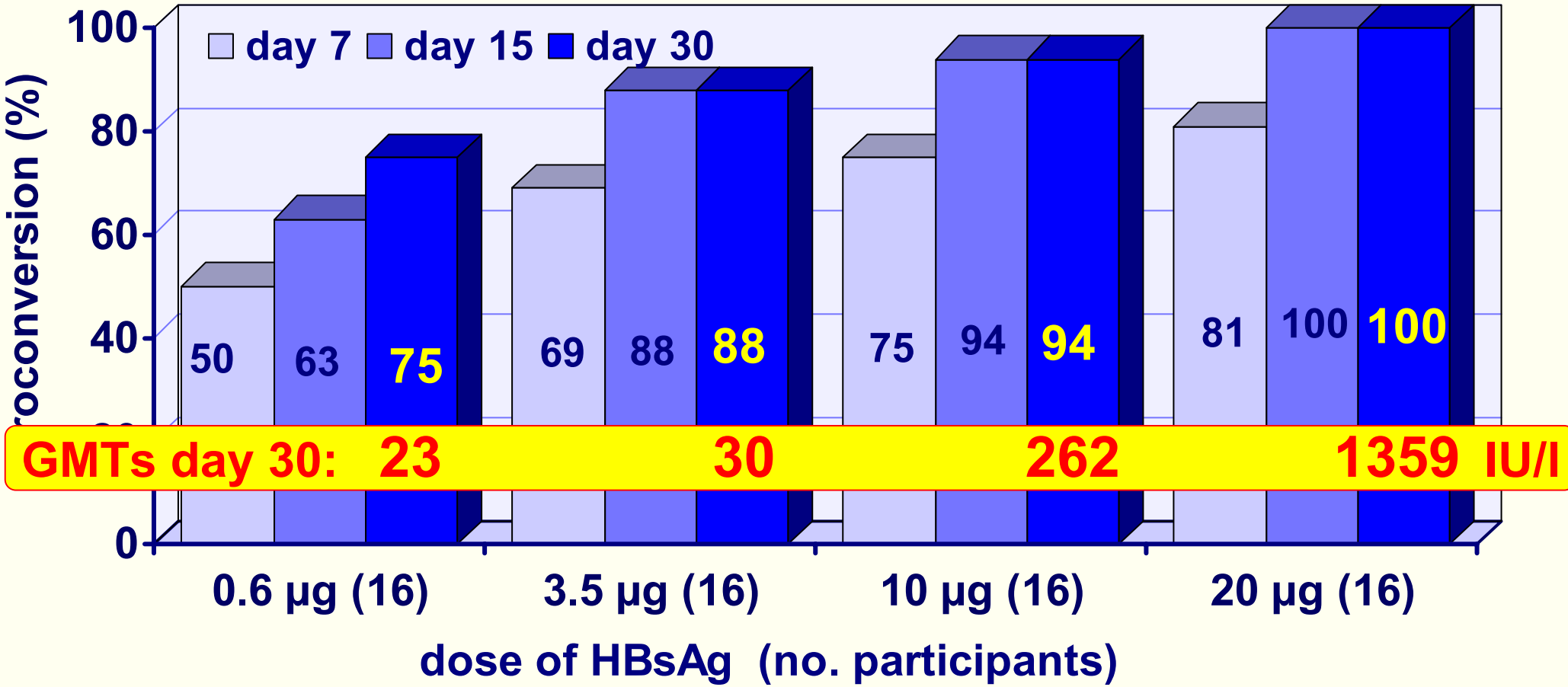


revaccination of 131 individuals 2-6 years after basic immuni-zation

anamnestic response to revaccination is correlated to primary response
but on a higher level

Jilg et al in Coursaget, Progress in Hepatitis B immunization 1990;p 419

anamnestic response to administration of non-absorbed HBsAg in responders to HB vacc. after loss of anti-HBs



Dentico et al Vaccine 2002;20:3725

anamnestic anti-HBs response after revaccination

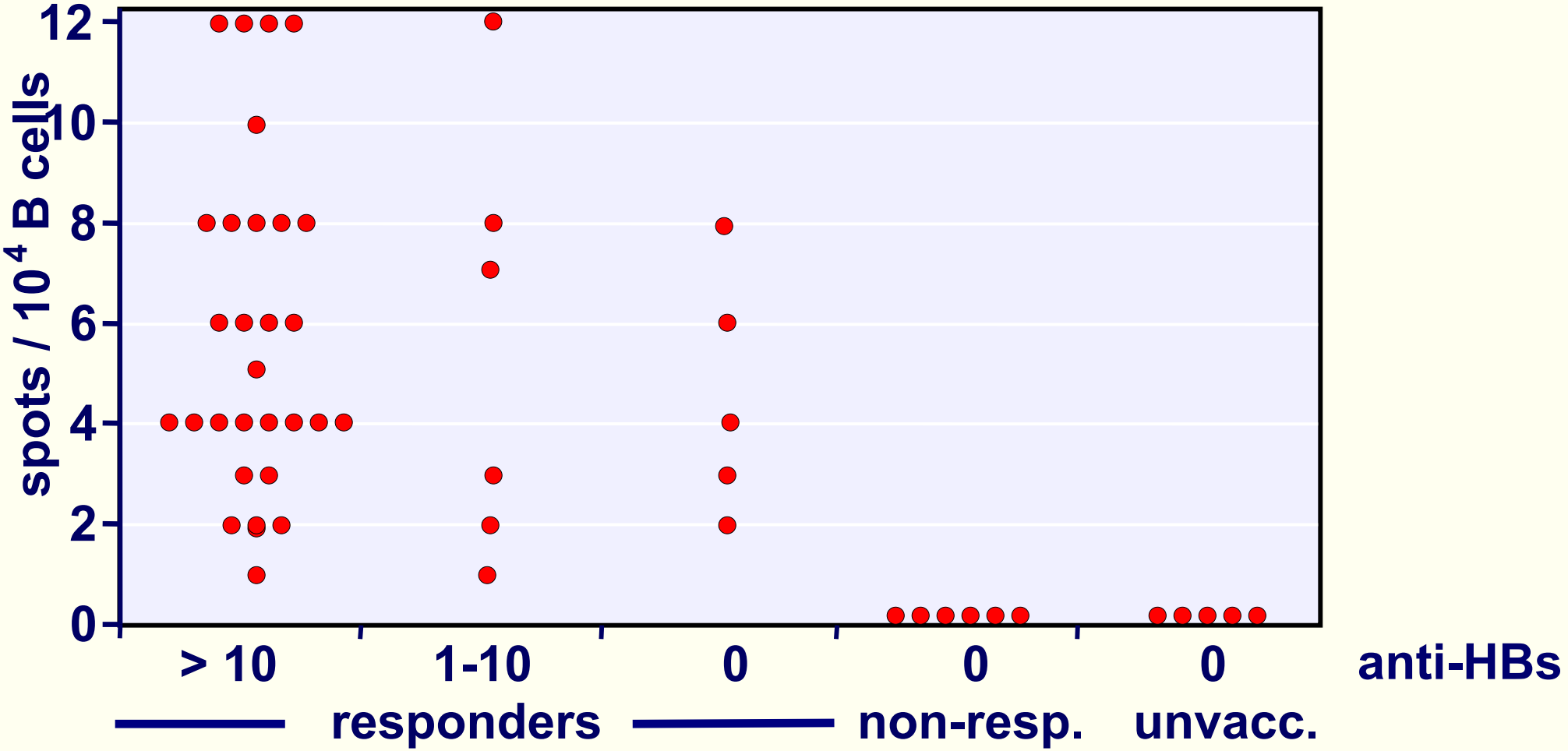
- present in >95% of vaccinees for at least 10 years after basic immunization
- correlated with primary response
- strength of response depends on antigen dose

methods to demonstrate immunologic memory after hepatitis B vaccination

- ***anamnestic anti-HBs response*** **after revaccination**
- **demonstration of *anti-HBs-secreting B-cells* in vitro (ELI-spot)**

in vitro anti-HBs production by B cells

after vaccination against hepatitis B (n=51)



van Hattum et al in Hollinger, Viral Hepatitis and Liver disease;1990; p 774

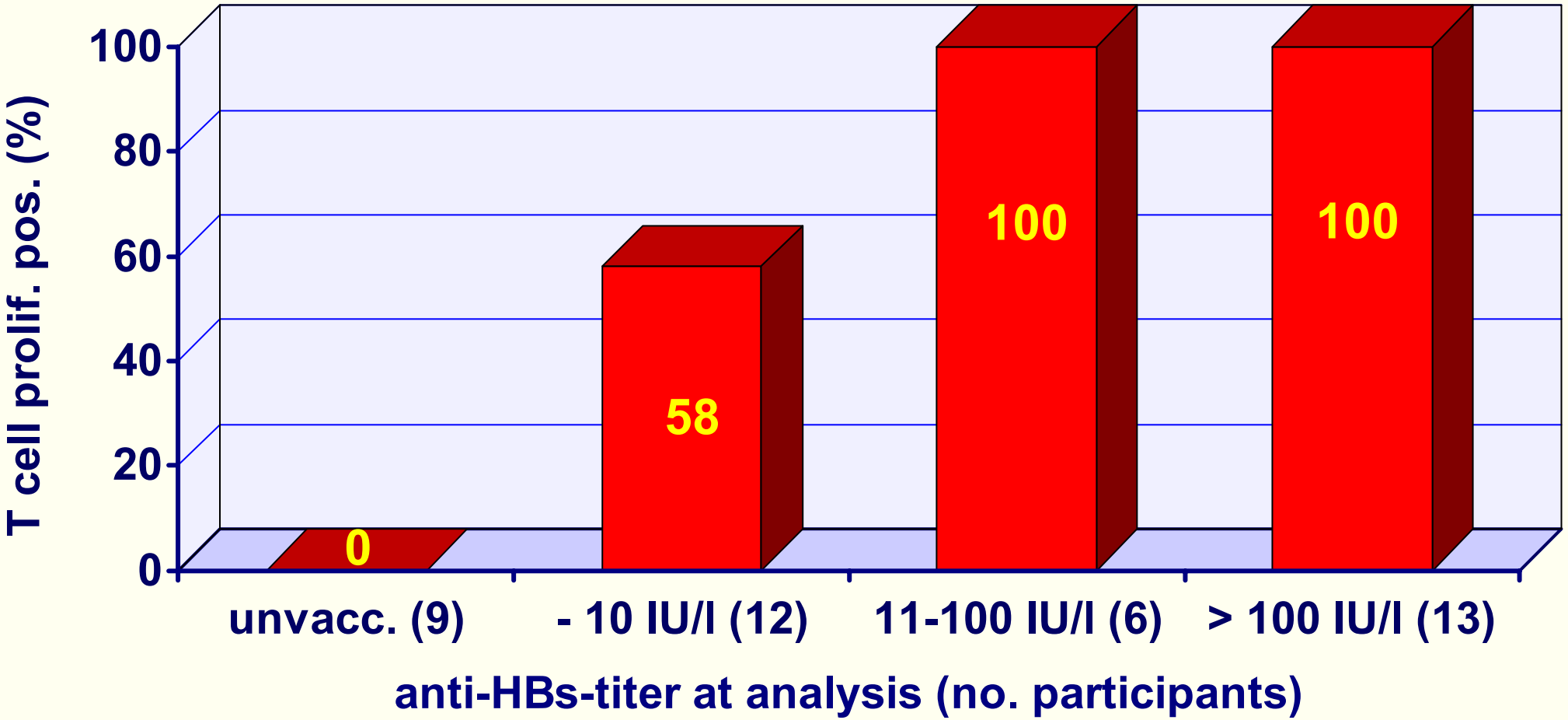
methods to demonstrate immunologic memory after hepatitis B vaccination

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

T cell proliferative response to HBsAg

in 31 HCW vaccinated 3-12 years before against hepatitis B

T cell proliferation positive individuals

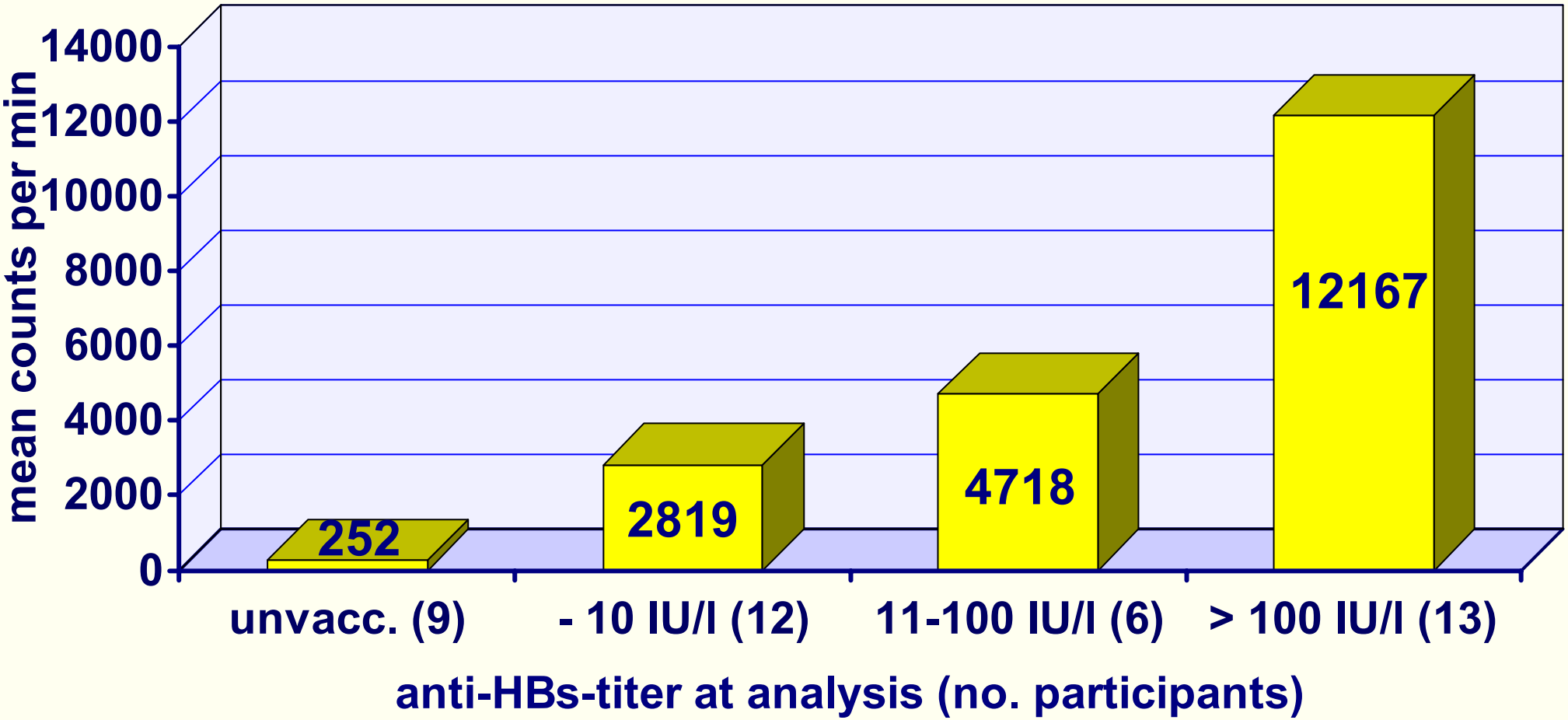


Wang et al World J Gastroenterol 2004;10:260

T cell proliferative response to HBsAg

in 31 HCW vaccinated 3-12 years before against hepatitis B

T cell proliferation: mean counts per minute



Wang et al World J Gastroenterol 2004;10:260

T cell immunity of Hep B vaccinees
before and after a booster 10 yrs after basic immunization

- 100 children (born to HBeAg pos. mothers) immunized at birth were tested after 10 years
- 21 (21%) were found to be negative for anti-HBs
- a subgroup was *tested for cellular immunity* by stimulation of PBMCs with HBsAg
- on revaccination *all showed a clear anamnestic anti-HBs response*

Huang et al Hepatology 1999;29:955

T cell immunity of Hep B vaccinees
before and after a booster 10 yrs after basic immunization

	before booster no. pos./no. tested	after booster no. pos./no. tested
T-cell proliferation	29/58 (50%)	27/46 (59%)
IL-2 production	42/52 (81%)	14/16 (87%)
IL-5 production	41/41 (100%)	13/13 (100%)

Huang et al Hepatology 1999;29:955

Immunologic memory after Hep B vaccination

- presence of HBsAg specific T- and B-cell memory in in succesfully vaccinated individuals documented for at least 10 years
- primary immune response seems to be a good predictor for the quality of immunologic memory *
- question about long term protection can only be answered by future long term follow-up studies looking for ***break-through infections*** and investigating the ***humoral and cellular basis for immunologic memory***

** Banatvala et al, Vaccine 2001: 19: 877*

difficulties in determining the length of protection

- follow-up studies with an observation time of >>10 years still rare
- number of vaccinees available for follow up decreases with time - data become less significant
- in low endemicity countries risk of hepatitis B very low - clinically significant break-through-infections (as sign of vaning immunity) will be rare
- immunologic memory so far mainly demonstrated by anamnestic response to revaccination - reliable and sensitive cellular tests only seldom used