Correlation between humoral and cellular immune responses after hepatitis A vaccination in low and high responder vaccinees

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„Low- or no-responsiveness“

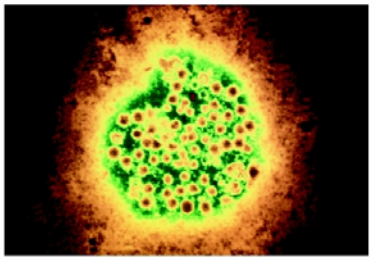
- Occurs in 2-10 % of vaccinees after routine vaccination
- Non responder rate is particularly high (10%) among hepatitis B vaccinees

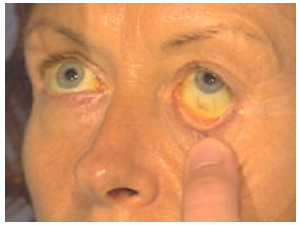
  Risk factors: age, gender, obesity, smoking, chronic diseases (diabetes, renal failure etc)

  Assoziation with HLADRB1; HLADQB1
- Low/no responsiveness is only defined on the basis of antibody levels
- The mechanisms of non-responsiveness are largely unknown

Questions to be answered:

- Is there a correlation between humoral and cellular immune responses in low responders?
- Are there characteristic changes of cellular parameters in low responders?
- Is there a cellular prediction marker of non-responsiveness?
- Are there consequences for vaccination recommendation?
- Is the infection risk higher in low/no- responders?
- Is low/no- responsiveness a generell or antigen-specific phenomenon?





Vaccine

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Persistence of seroprotection 10 years after primary hepatitis A vaccination in an unselected study population

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Study Design

Study population:

1016 healthy female and male adults; no upper age limit
(≥15 years at the time of primary vaccination)

Vaccine:

Havrix® 720 El.U (GSK)
0, 1, 6-12 months (i.m)

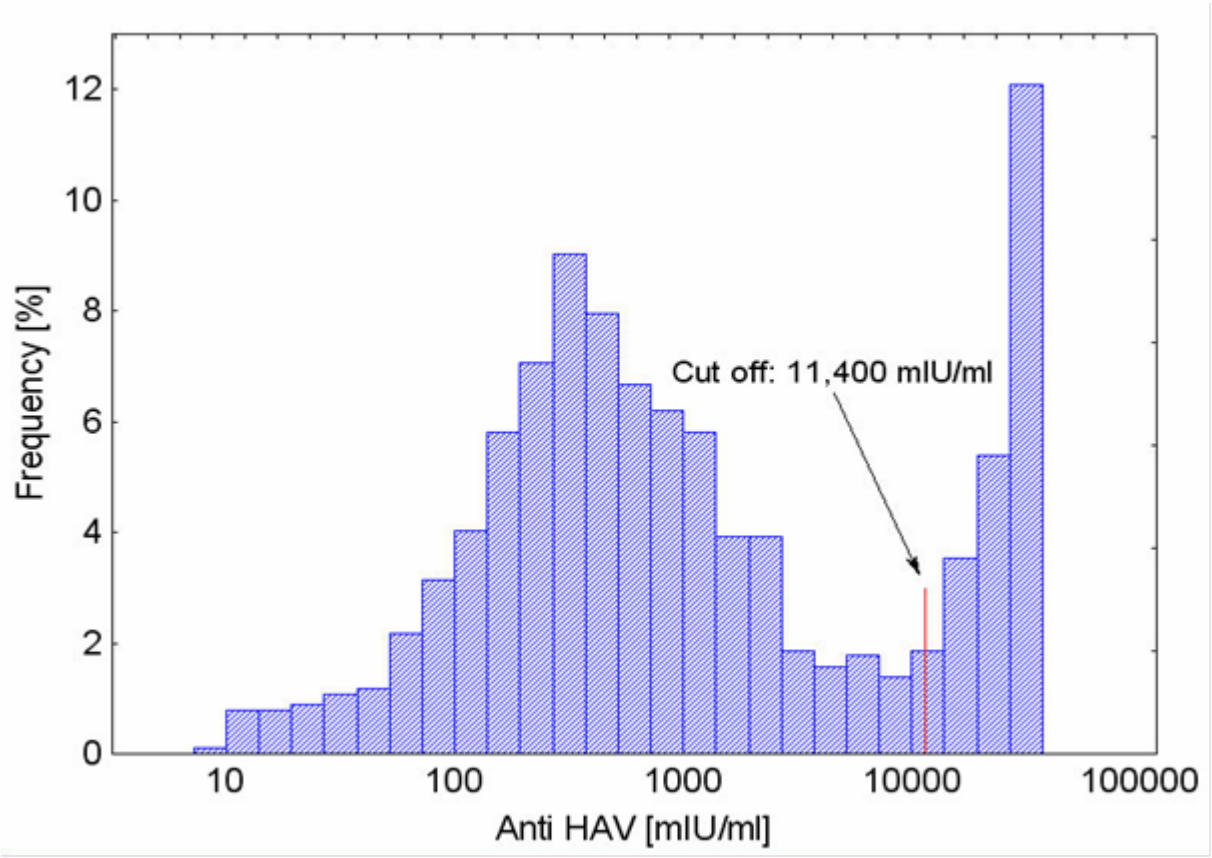
Control of immune responses (serology):

January 2003 to April 2006

Serology:

- ELISA (Anti-HAV Elecsys, Roche, Institute of Virology, MUW)
- Enzygnost HAV-ELISA (Dade Behring; ISPTM)
- Anti-HAV Titer Cut-Off: 10mIU/ml

Distribution of antibody titers (n=1016)

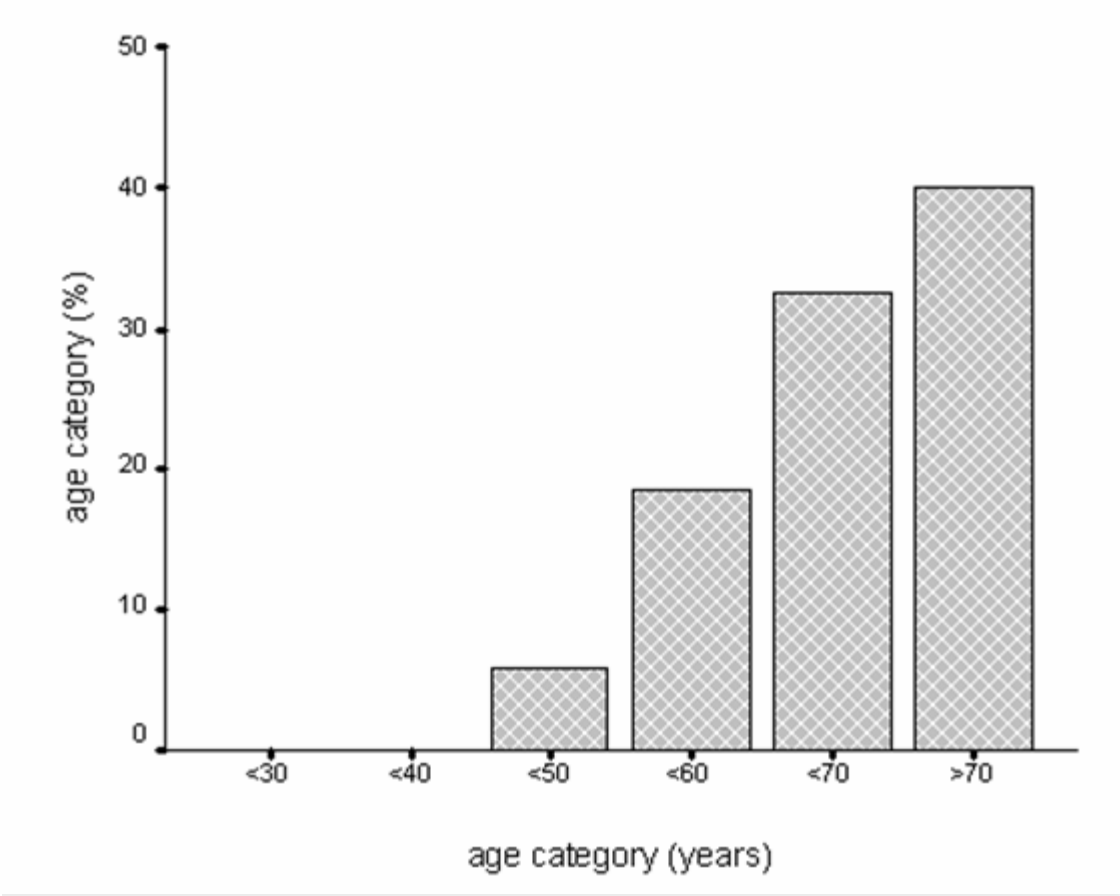


Rendi-Wagner, Vaccine 2007

Study population

	Total	Anti-HAV < 11400 mIU/ml	Anti-HAV >11400 mIU/ml
n (%)	1016 (100)	796 (78,35)	203 (19,98)
Age	54,67 (±12,95)	52,51 (±13,17)	63,23 (±7,72)
Interval	9,9 (± 0,81)	9,88 (±0,8)	10,09 (±0,81)
gender (f)	52,9	51,8	56,2
Smoker/n-smoker (%)*	9,94/50,6	10,3/48,49	9,35/60,1
BMI (± SD) (n= 863)	25,31 (± 4,15)	25,17 (±4,13)	25,41 (±3,53)

Age category of hepatitis A immune subjects due to infection (> 11400 mIU/ml; n = 203)



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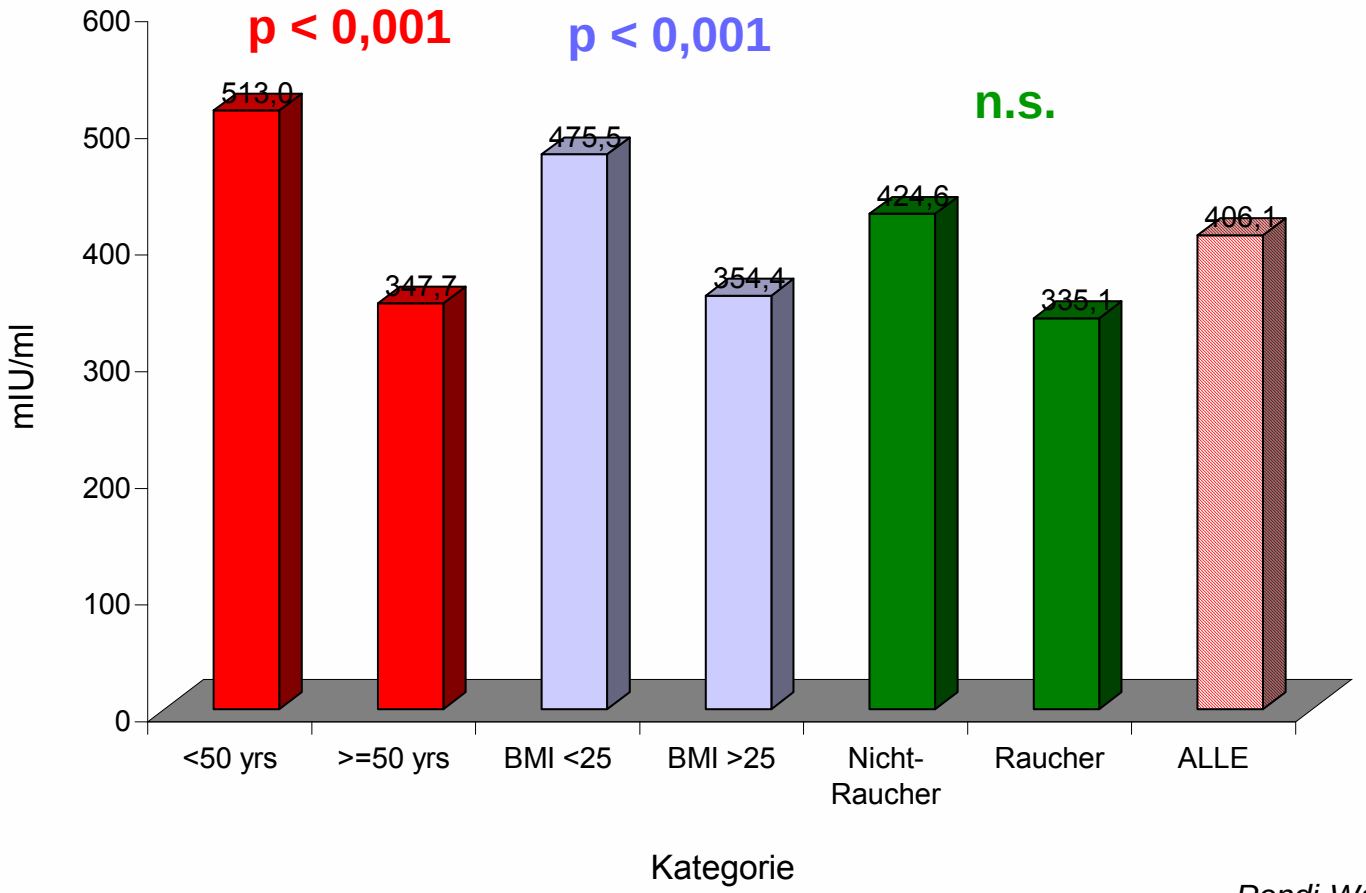
Vaccine induced GMTs according to categories (< 11400 mIU/ml, n = 796)



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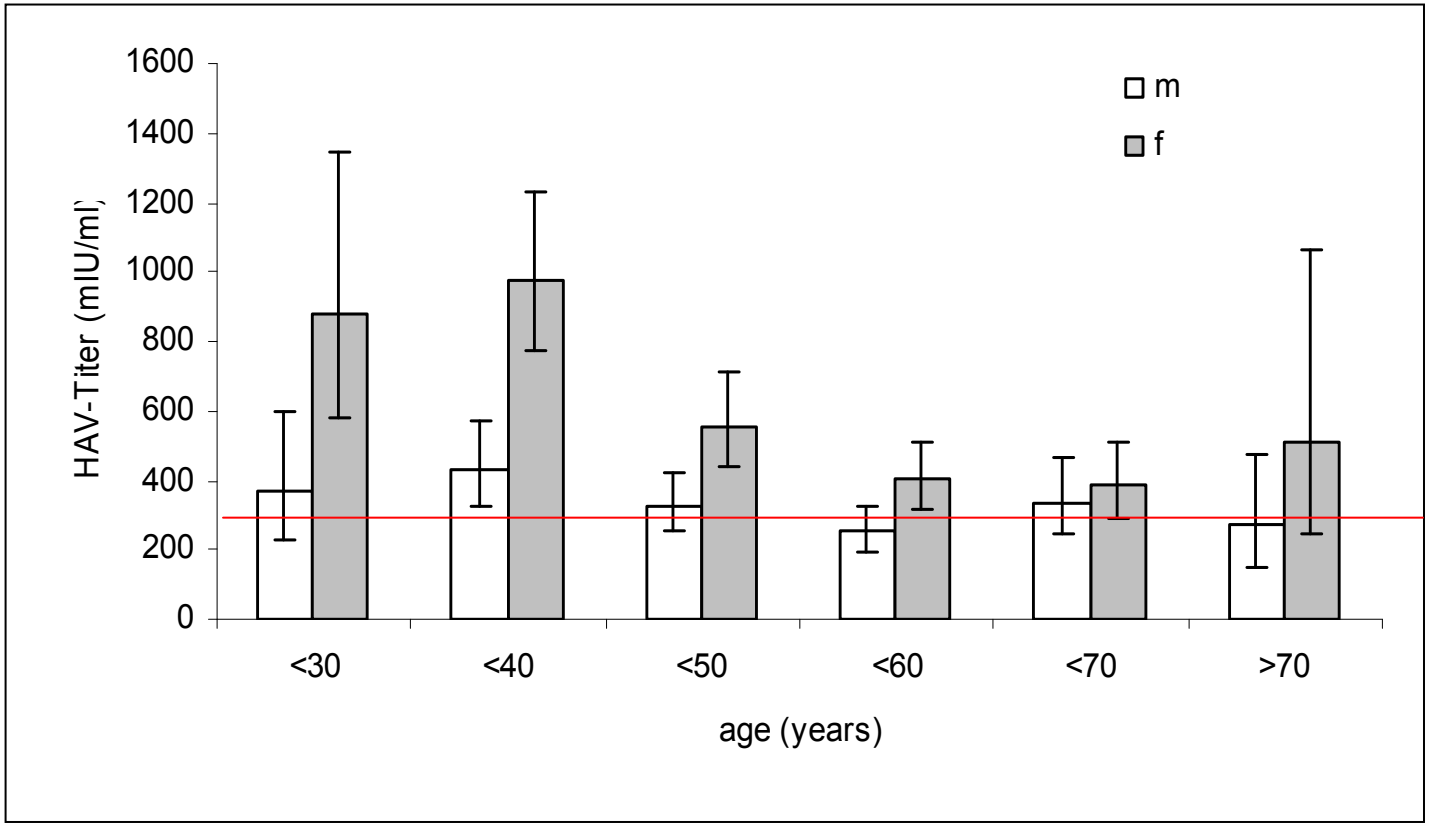
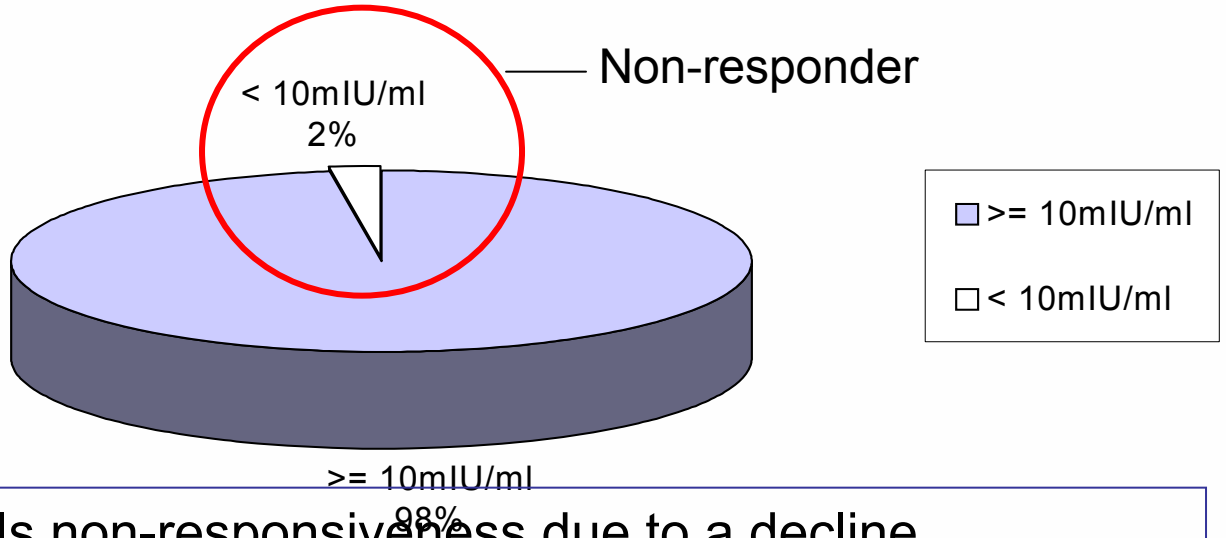
Vaccine induced, gender-specific GMTs 10 years after primary vaccination



After 10 years GMTs are far above protective range – New booster recommendation: 20 years!

Vaccine induced seroprotection rate (n= 813)



Is non-responsiveness due to a decline of antibodies or due to an intrinsic inability to respond to hepatitis A antigen?

SPR nach Alter (j)	%
<50 Jahre	98,1
>50 Jahre	97,8

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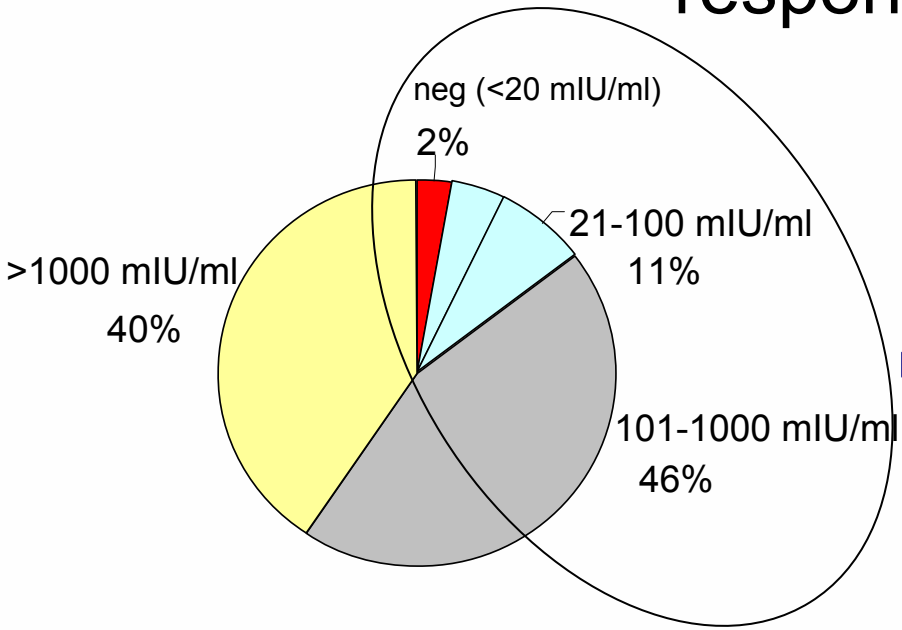
Immunological characterization of Low/no responsiveness



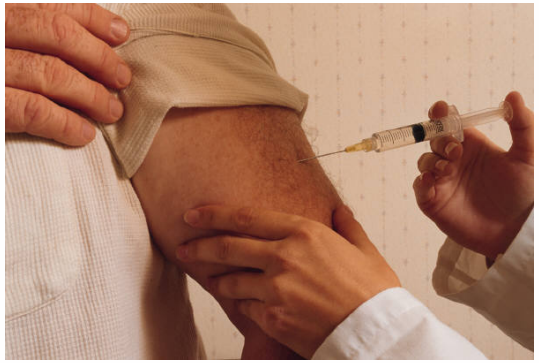
3 Groups (n=52):

GROUP 1 (n=10): < 20 IU/l

GROUP 2 (n=26): 21 – 100 IU/l

GROUP 3 (n=16): 101-1000 IU/l

Booster with Havrix 1440



Blood pre and 7 days after booster

Mean age:
Group 1: 61,4 yrs
Group 2: 63,3 yrs
Group 3: 54,5 yrs

Detailed immunological characterization of low/no-responsiveness after hepatitis A vaccination

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Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Correlation between humoral and cellular immune responses and the expression of the hepatitis A receptor HAVcr-1 on T cells after hepatitis A re-vaccination in high and low-responder vaccinees

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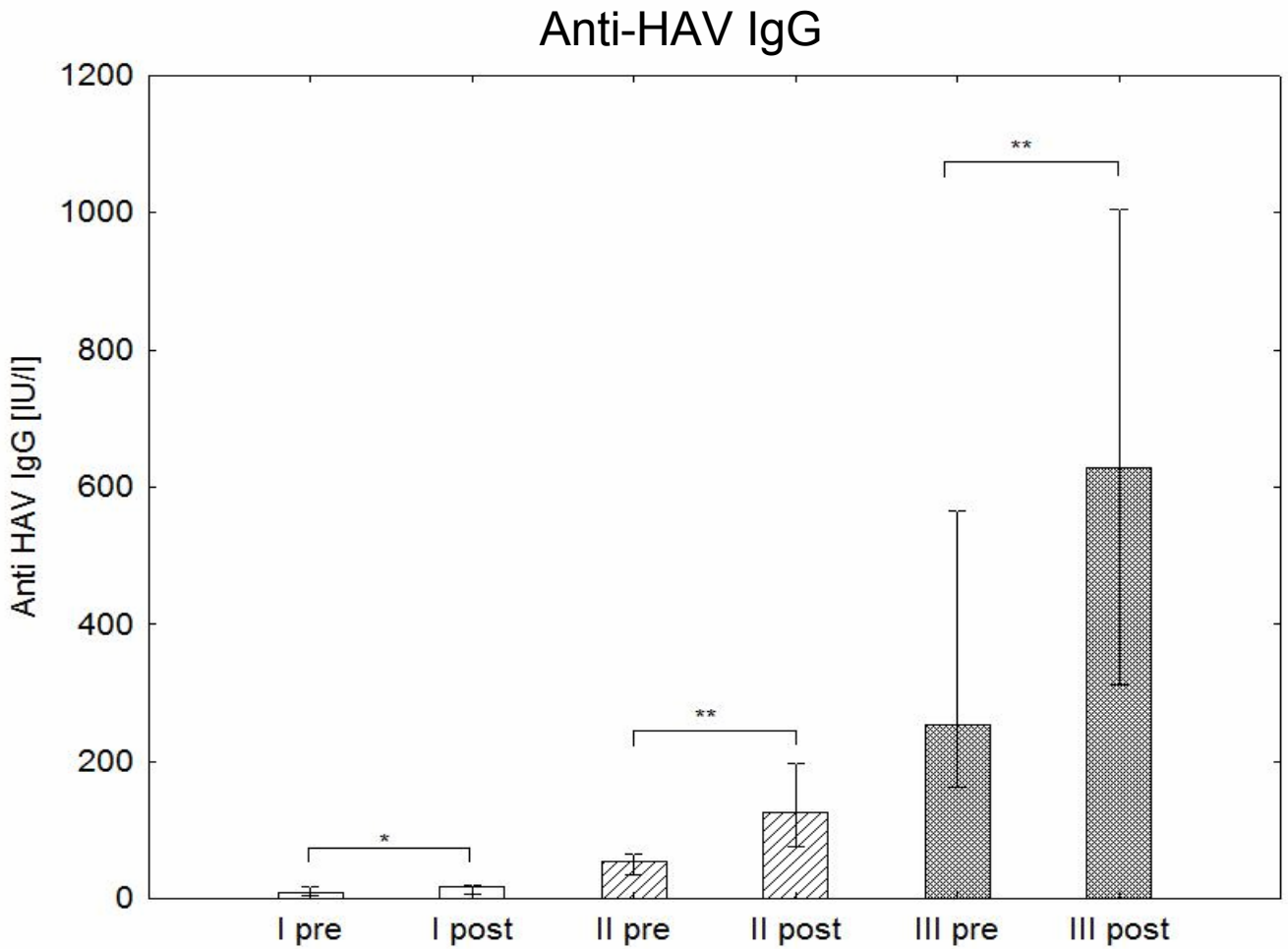
Humoral immune responses pre and post hepatitis A booster



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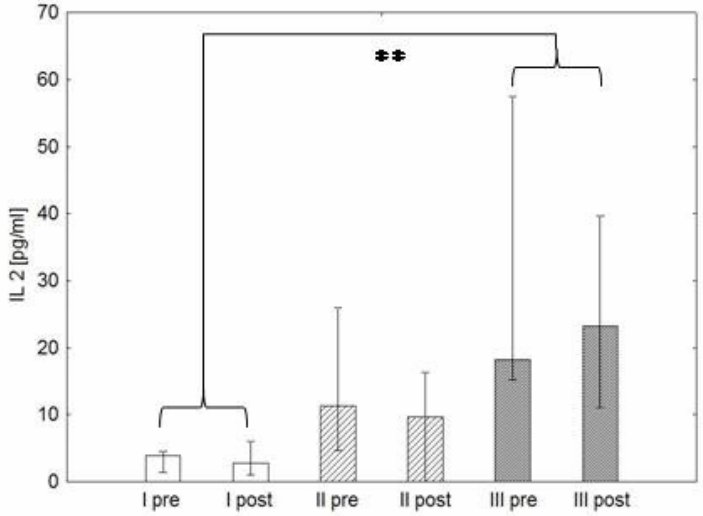
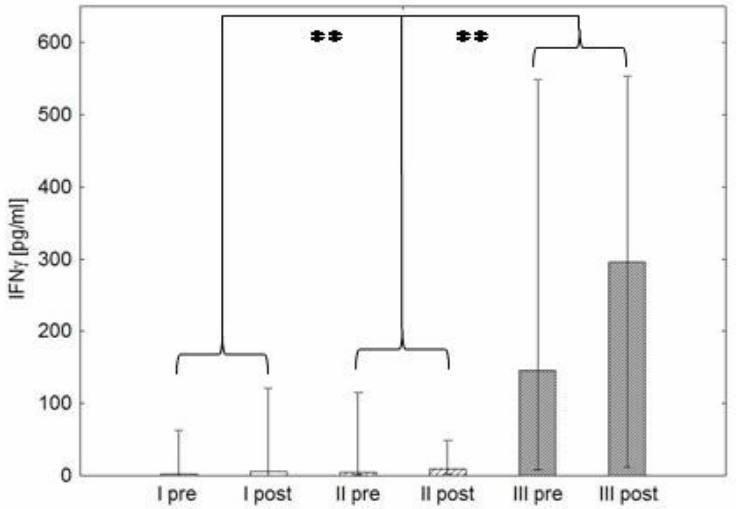
Cellular immune responses pre and post hepatitis A booster

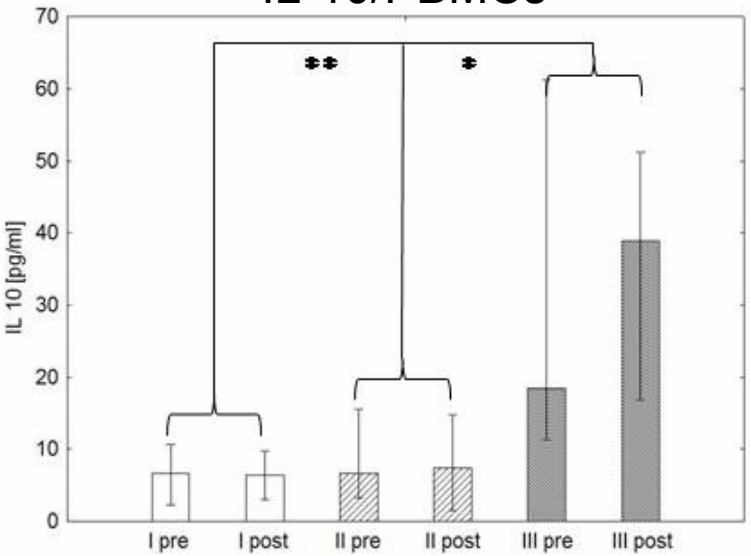
IL-2/PBMCs*



IFN-γ/PBMCs



IL-10/PBMCs



*PBMCs were stimulated with HAV antigen; Cytokine production measured in supernatants

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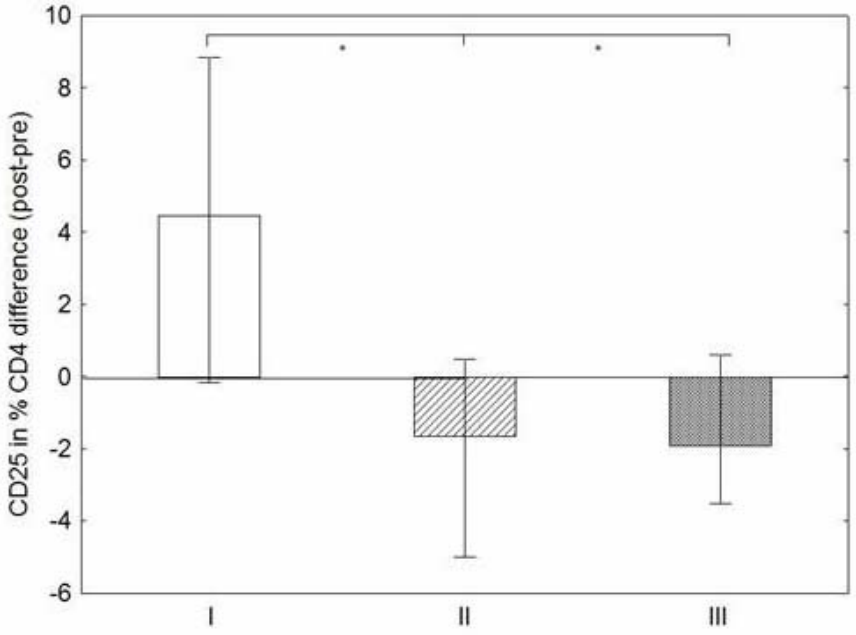
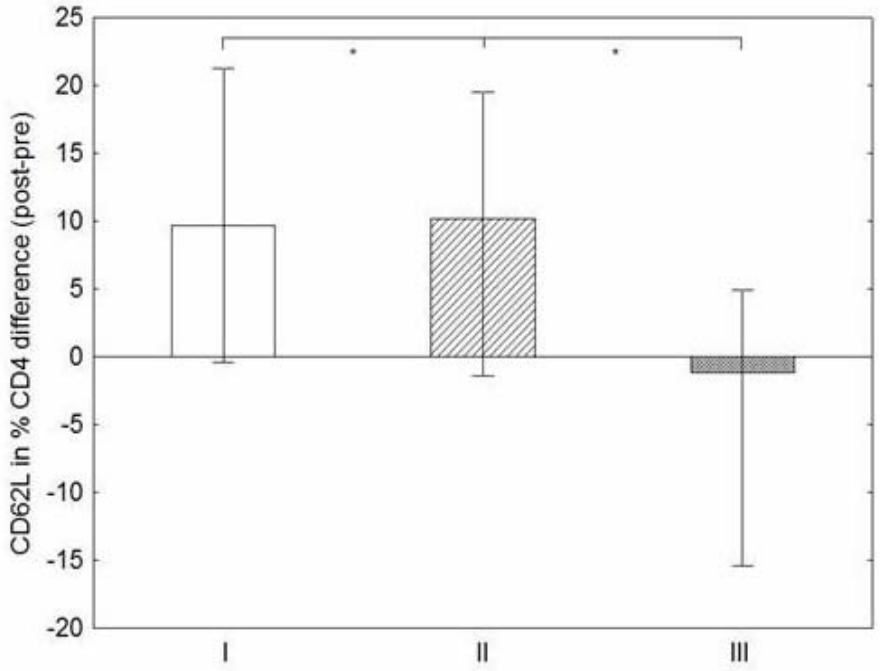
Changes in T cell surface marker expression after booster vaccination

CD4+CD25+ T-cells after booster vaccination



CD62L+ on T cells after booster vaccination



Interpretation: in an attempt to overcome non-responsiveness, new/naive T-cells are being activated

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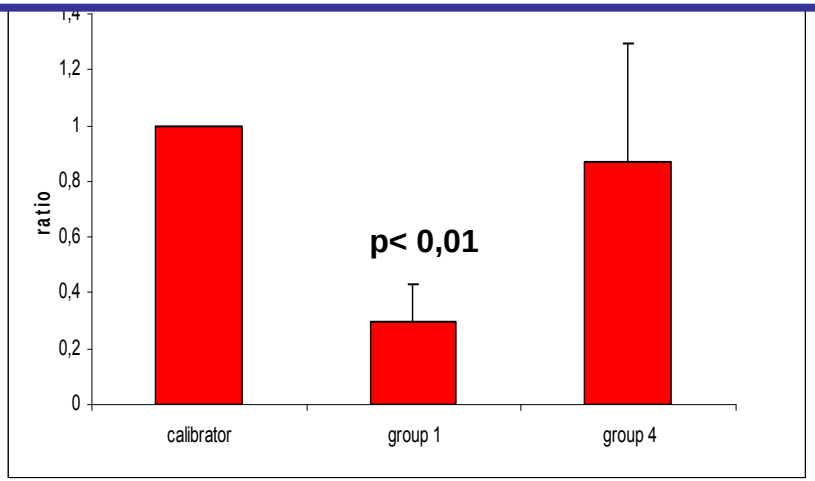
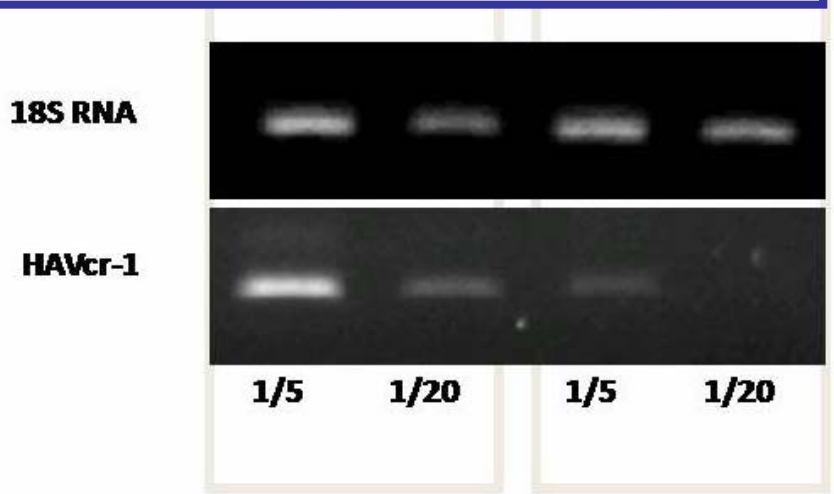
Expression of the HAV receptor on T cells

HAV receptor as possible cellular prediction marker of non-responsiveness against hepatitis A?





HAV receptor expression is significantly lower on T cells of non-responder than on T cells of high responder

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Summary of immune parameters in non- and higher responder vaccinees

		Anti-HAV Ig (IU/l)	HAVcr-1 Ratio	HAVcr-1/CD4 Ratio	IFNγ (pg/ml)	IL-2 (pg/ml)	IL-10 (pg/ml)	(%) CD4	% CD62L of CD4	% CD25 of CD4	%CD4/CD25^{high}
N1	Pre	7,2	0,42	10,35	7,6	0	31	41	24,5	43,9	4,54
	Post	11,4	0,31	6,29	8,8	8,4	45	50	40	34	4,67
N2	Pre	0,1	0,13	6,51	2,08	4	6	20,9	31	42	3,23
	Post	19,3	0,18	6,10	6,3	9	14	30	29	52	3,88
N3	Pre	0,1	0,34	9,79	0,9	2,2	15	34,6	21,6	12,6	0,38
	Post	0,1	0,26	5,69	1,1	1,5	10	45	42,6	15,2	0,69
H1	Pre	555,9	2,24	55,88	248,5	7,5	10,6	40,0	45,0	60,0	1,51
	Post	1031,0	1,79	41,25	3000	18,1	25,9	43,5	55,2	61,2	1,91
H2	Pre	598,5	1,24	21,49	830	92,5	68,0	57,7	33,7	53,4	3,76
	Post	1115,0	0,91	17,98	831	43,9	63,9	50,6	37,4	51,5	3,84
H3	Pre	266,5	3,98	86,33	209,6	23,4	138,1	46,1	20,1	55,4	3,15
	Post	1488,0	1,57	32,71	515	32,0	144,5	47,9	20,2	51,6	2,62

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Conclusions

- National recommendation for 20 year hepatitis A booster interval in Austria (travellers)
- A small, but significant, percentage of „real“ hepatitis A non-responder
- Routinely performed immune response evaluation is not necessary, but
- Risk populations (frequent travellers, health care professionals, travellers staying for prolonged time in endemic areas) should be carefully observed!
- The hepatitis A receptor might function as a cellular prediction marker of non-responsivens in risk populations