

Response to Booster Dose in Children Immunized with Hepatitis B Vaccination at Birth in Alaska



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Declarations and Off Label Use of Medications

- Declarations: None

Persistence of Anti-HBs and Booster Response in Children Immunized in Infancy

- Studies on the prevalence of anti-HBs levels in children at a given age after infant HB immunization differ widely
- Proportion of children with anti-HBs level \geq 10mIU/ml (protective level) at a given age is influenced by multiple factors including:
 - Peak Level of anti-HBs after last dose
 - Exposure to HBV

Peak Level of Anti-HBs after Age of First and Last Dose of Vaccine

- Date when 1st dose administered:
 - Higher if 1st dose given after 2 months of age than at birth
- Total number of Doses administered:
 - 4 doses > 3 doses > 2 doses
- Strength of each dose and type of vaccine
 - 10 mcg > 5 mcg > 2.5 mcg
- Spacing of dosages:
 - Higher if last dose given at 12 vs. 6 months of age

Environment Infant is Born Into: Natural Boosting

- Mother HBeAg-positive vs. HBeAg-negative
- Presence of HBsAg-positive persons in household
 - HBeAg positive vs. HBeAg-negative contacts
- Prevalence of HBsAg-positive persons in community:
 - Proportion children vs. adults
 - Proportion HBeAg-positive vs. negative
 - HBV predominant genotype.

Median Age of HBeAg Seroconversion by Genotype: Median 21 Years Follow-up*

Genotype	No. HBeAg+	Age 50% lost HBeAg	Age 75% lost HBeAg
A ₂	34	19.8	32.1
B ₆	6	19.5	27.5
C ₂	36	47.8	58.1
D	305	18.0	27.3
F ₁	126	16.1	24.5

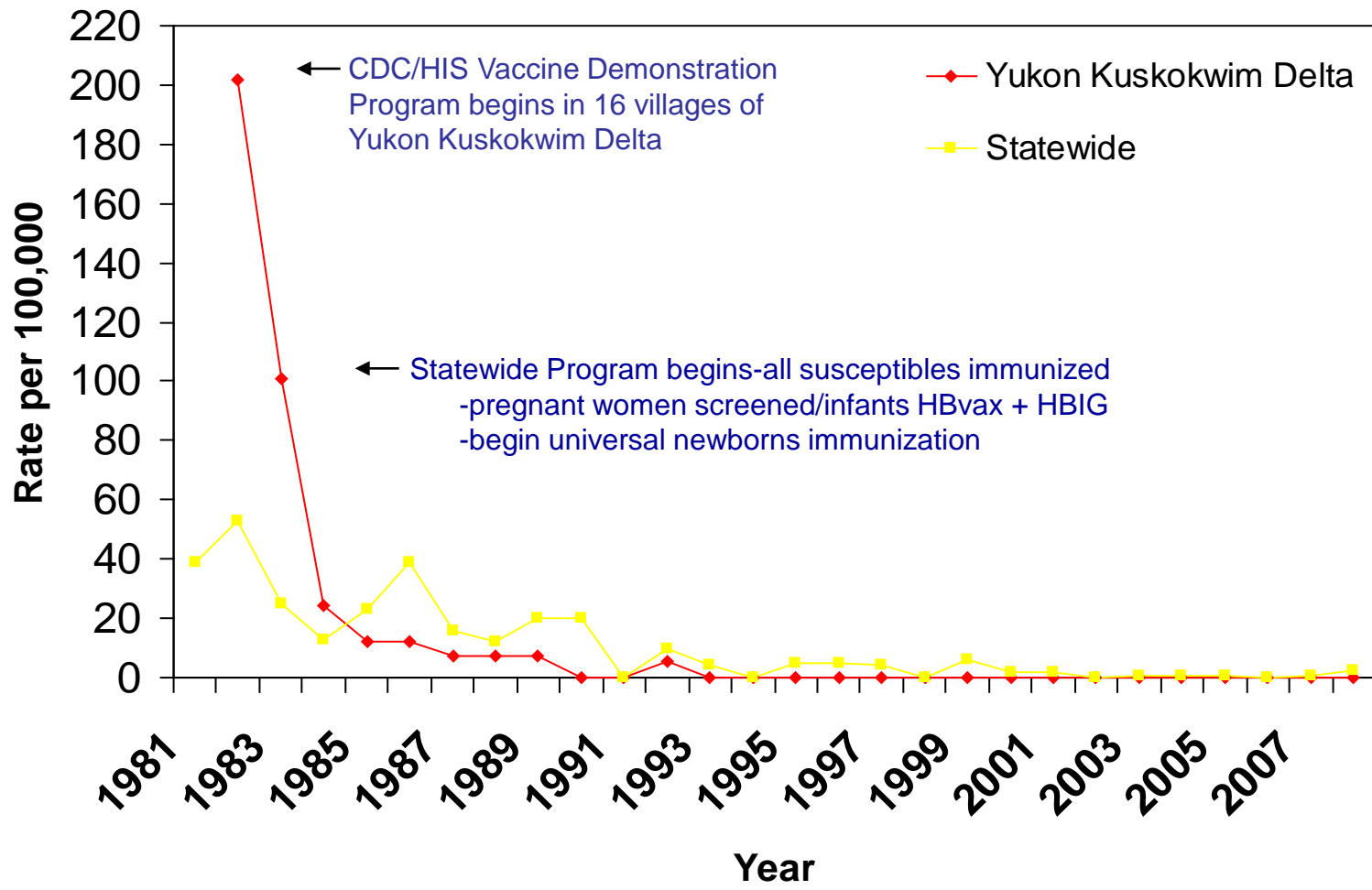
Changing Pattern of HBV in Alaska

- Western Alaska went from a high endemic area prior to 1984 to an intermediate endemic area after 2000 due to:
 - Introduction of universal newborn HB immunization in 1984
 - Massive catch-up vaccination program in children and adults 1984-1988
 - 53,000 persons (90% of population in endemic areas) screened and 40,000 vaccinated
- Marked change in infectivity of chronic HBV carriers between then and now

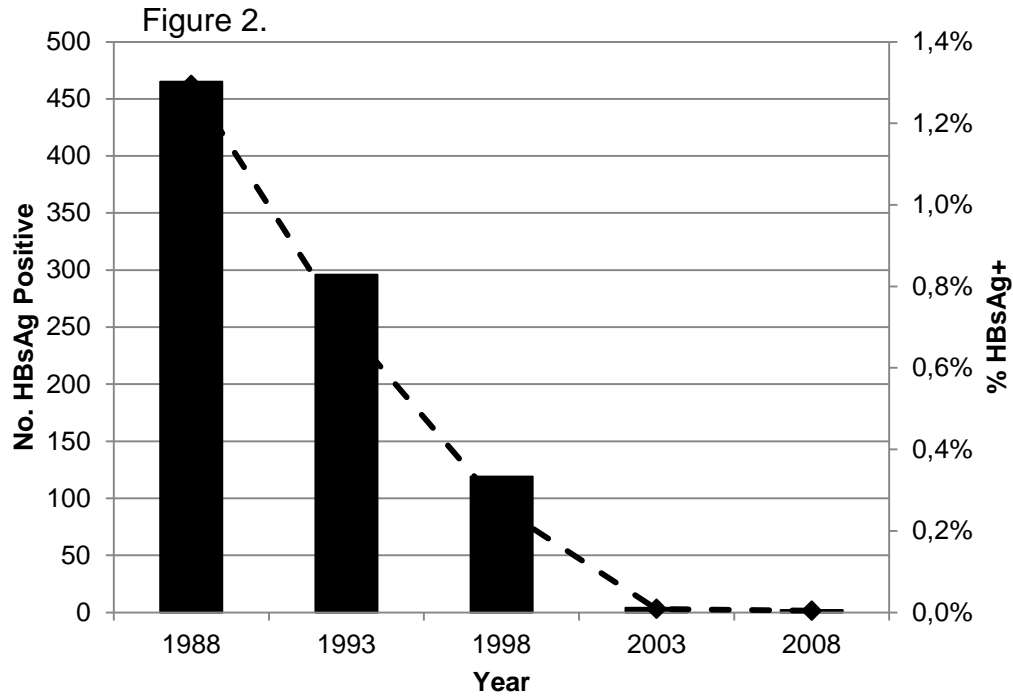
Rapid Drop in Transmission of HBV

- Elimination of acute hepatitis B in children
 - Elimination of HCC in children
- No HBsAg carriers < 20 years of age in 2011
- Prevalence of HBeAg in HBsAg-positive adults and children has fallen from 40% to ~1%

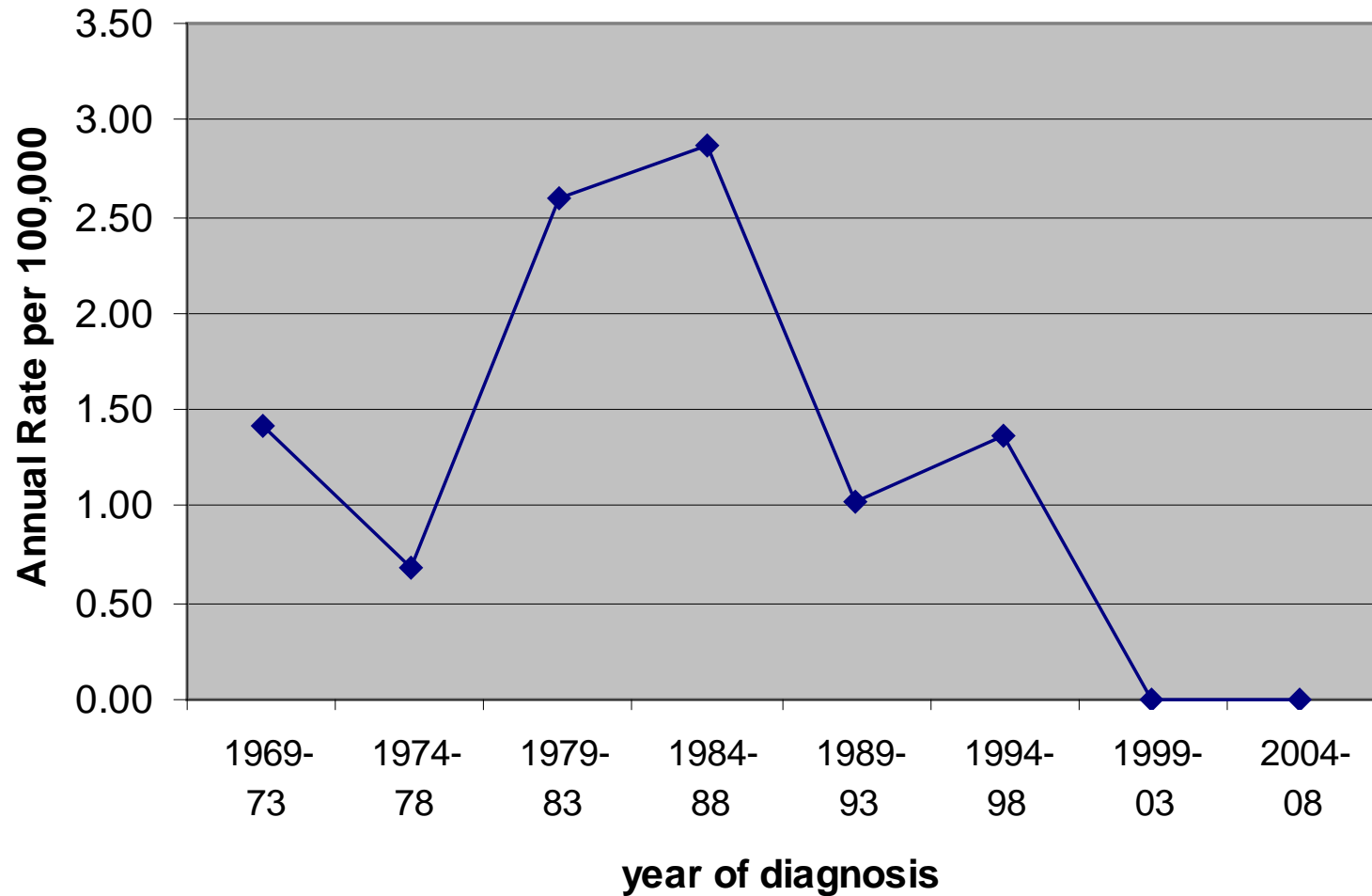
Incidence Symptomatic Hepatitis B in Alaska Native Peoples 1981- 2008



Number of HBsAg-positive Alaska Native Children Under 20 Years of Age: 1988-2008



HCC in Alaska Natives <20 years of age



P value for trend = 0.002

Natural Boosting in Alaska

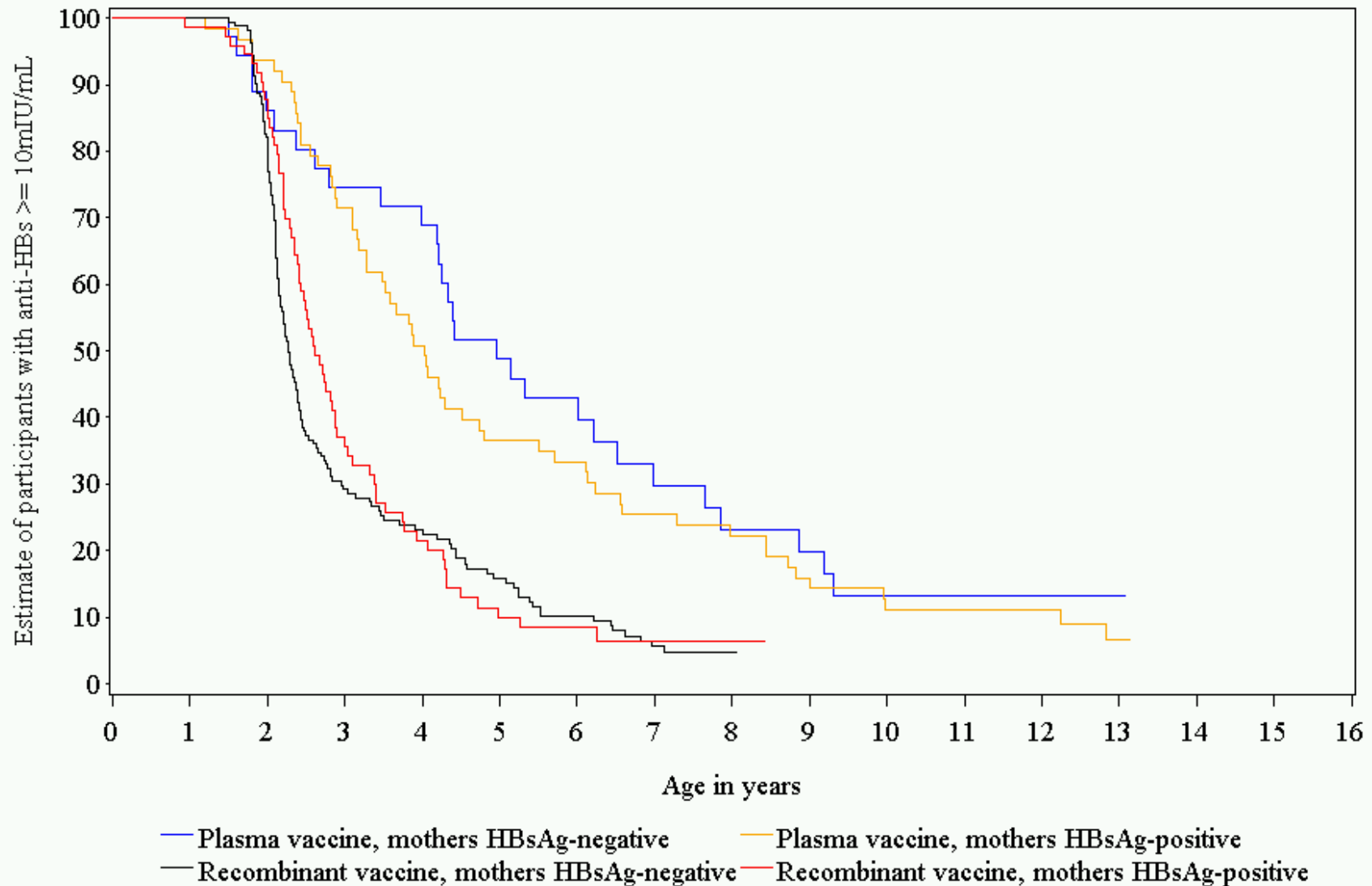
- Defined as a 4 fold rise in anti-HBs without anti-HBc in Vax Demo study presented earlier
- Only measured during the first 10 years after immunization.
- Evidence of natural boosting found in 8.2% of 1530 persons followed during this period
 - Prevalence of natural boosting likely to have decreased since number of anti-HBc breakthrough infections fell from 25 between first 15 years to 0 between 15 and 22 years

Hepatitis B Long-Term Immunogenicity in Newborns Vaccinated in Alaska

- Multiple studies from Alaska have shown that anti-HBs levels fall faster in those immunized at birth than those immunized as children or adults
- <5% given recombinant and <15% plasma vaccine have anti-HBs \geq 10 mIU/ml at 10 years of age
- Only about 50% have a booster response at older adolescence

Long Term Persistence of Anti-HBs In Alaska Native Children Immunized At Birth

Anti-HBs Persistence by Vaccine Type and Maternal Status



Long-term Efficacy of HBV Vaccine Administered in Infancy: Alaska Study

- 6 children had an HBV breakthrough infection
- None of these children were symptomatic or became HBsAg positive
- 2 of these had HBV DNA transiently

Alaska Booster Dose Studies in Children Given Recombinant Hepatitis B Vaccine Starting at Birth

Age at Boost Moms HBV neg	% anti- HBs >10	No. Boosted	No. (%) response
5 years*	12.5%	134	90%
5-7 years**	29%	158	99%
7.5 years*	0%	35	91%
10-15 years**	5%	138	88%
15 years^	0%	35	51%

*Peds Infect Dis J 2004;23:650-5, **Pediatrics 2007;120:373-381

^Vaccine 2007;25:6958-64

Alaska Booster Dose Studies in Children Given Plasma Hepatitis B Vaccine Starting at Birth

Age at Boost	% anti-HBs	No. Boosted	No. (%) response
9 years Mom HBV-neg	41%	54	33 (67%)
12 years Mom HBV+	31%	10	9 (90%)
13 years Mom HBV-neg	24%	12	8 (67%)
12-15 years Mom HBV-neg	21%	74	71%

Yo-Hep Booster Dose Study

- **378 Children who received 3 doses of hepatitis B vaccine:**
 - **Dose #1** birth to 7 days, **dose #2** 6 weeks to 12 weeks, **dose # 3** 6- 9 months.
- **Three Groups:**
- **CR:** 166 Children who received recombinant vaccine as primary series 5-7 years ago
- **AR:** 138 Adolescents who received recombinant vaccine as primary series 10-14 years ago
- **AS:** 74 Adolescents who received serum-derived vaccine as primary series 10-14 years ago

**Proportion with an anamnestic anti-HBs response
by age, at 2 weeks after a booster dose of hepatitis B vaccine,
among persons with baseline anti-HBs <10 mIU/mL**

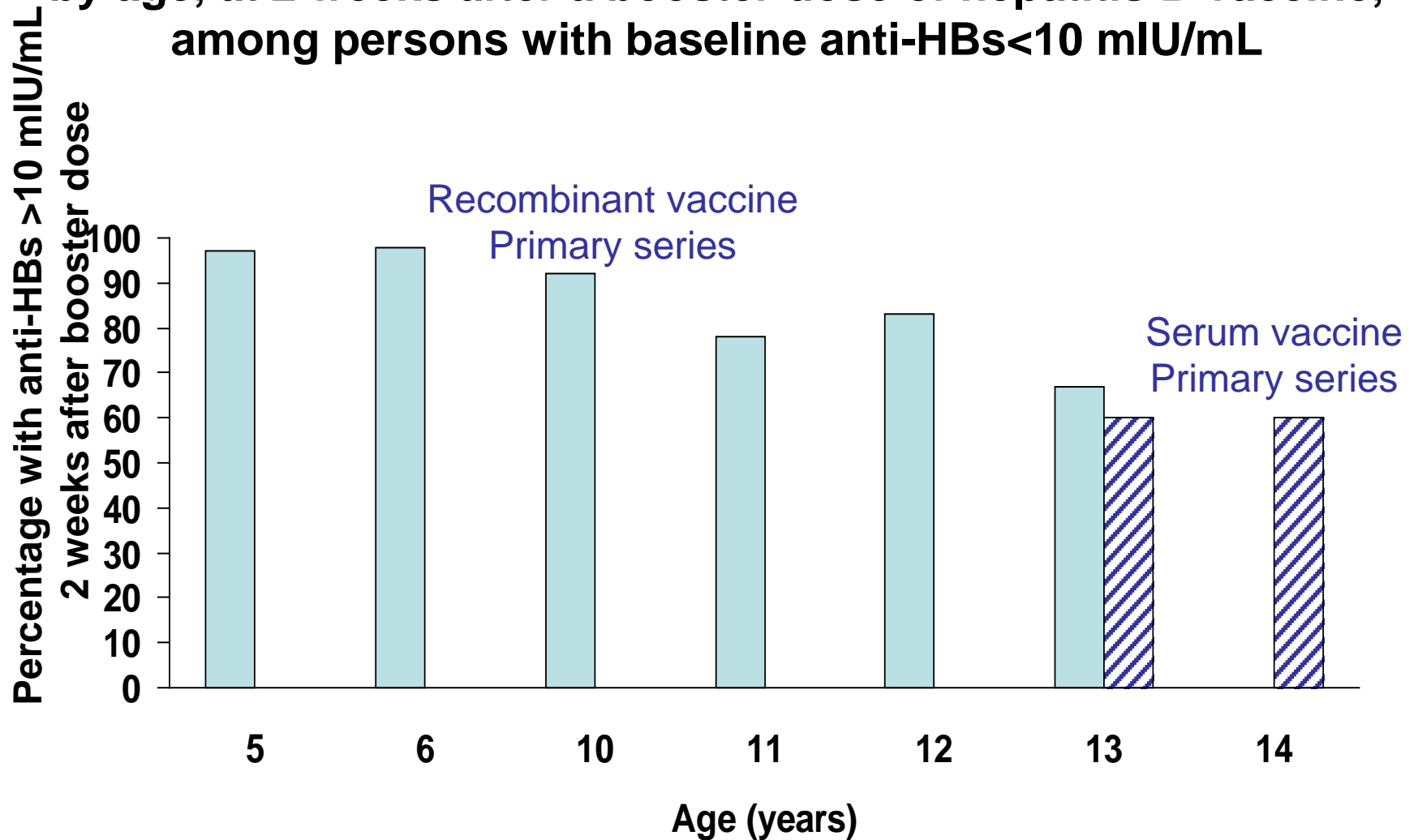
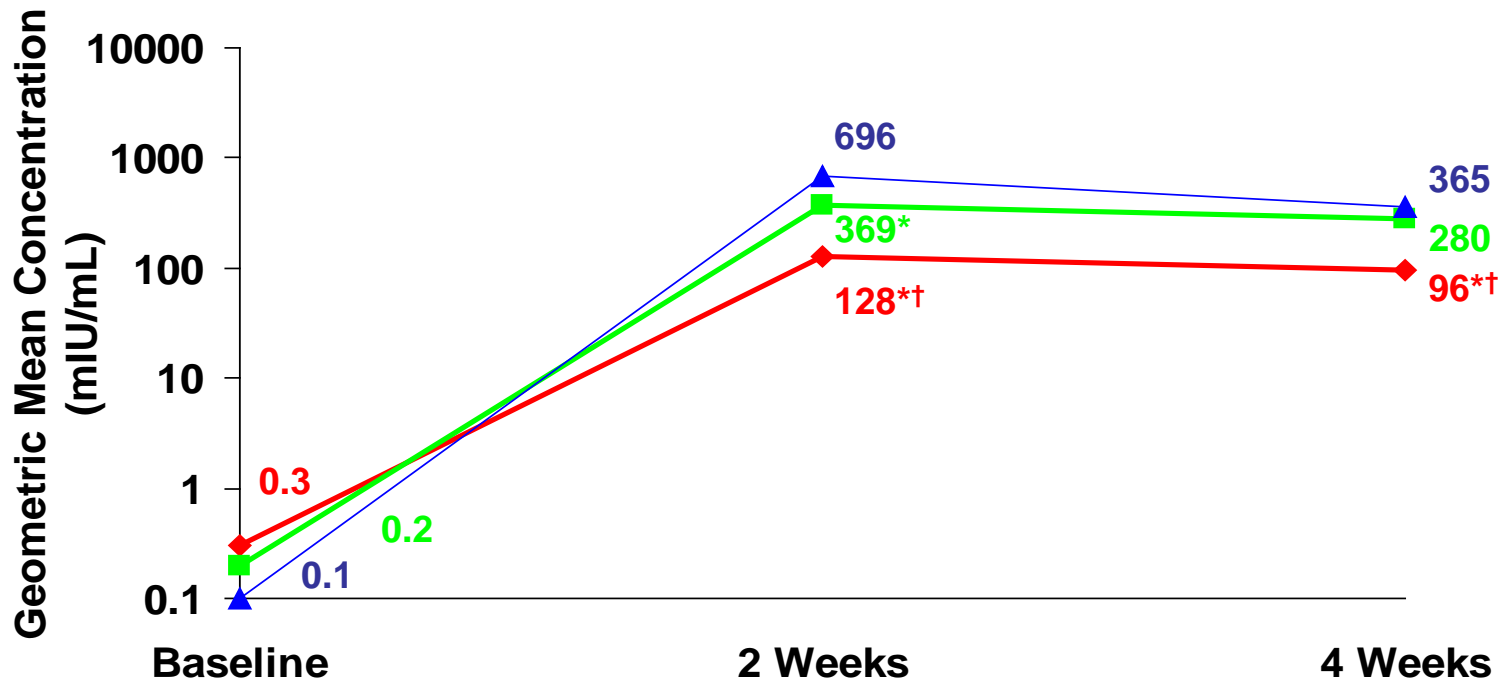


Figure 2b. Anti-HBs (GMC) at 2 and 4 weeks after a booster dose among participants with an anamnestic response (non-responders excluded), baseline anti-HBs <10 mIU/mL, by group



Differences between groups within each figure:

*Significantly less than **CR** group GMC at this timepoint

†Significantly less than **AR** group GMC at this timepoint

‡Significantly less than **AS** group GMC at this timepoint

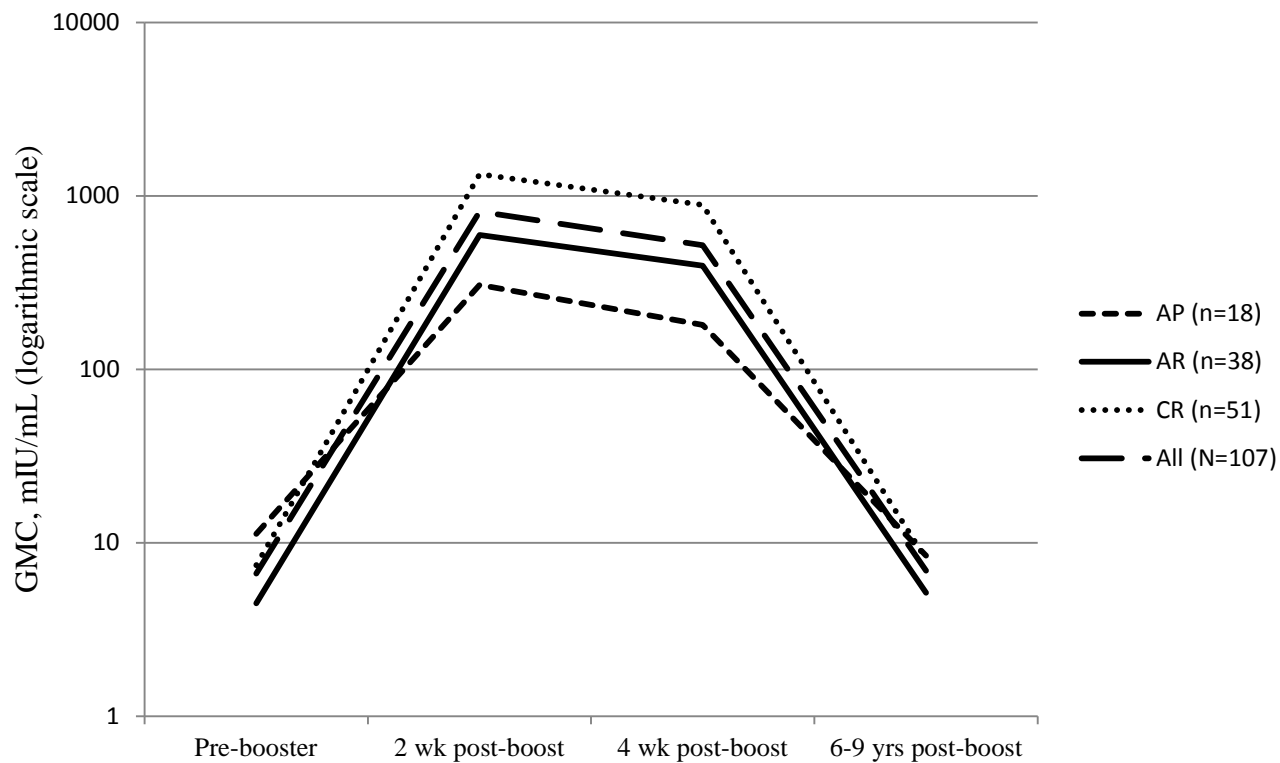
Yo-Hep follow-up Study in Children Who Received Booster Dose 6-9 Years Previously

- 107 Children divided into 3 groups were tested: All had responded to a booster dose
 - Group 1 received 2.5 mg doses recombinant boosted at 5-6 years of age
 - Group 2 received 2.5mg doses recombinant vaccine at ages 10-12 years
 - Group 3 received 10 mcg plasma-derived vaccine at 13-15 years
- 60% anti-HBs was < 10 mIU/ml at 6-9 years

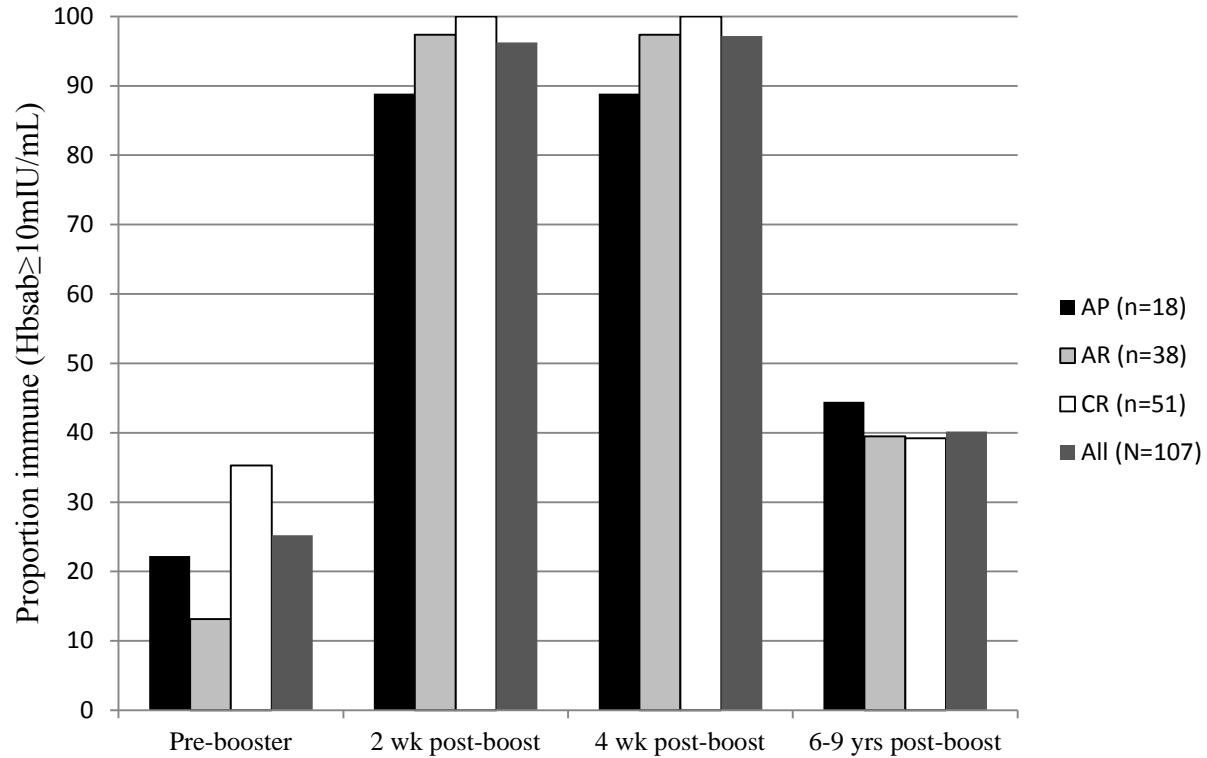
Yo-Hep Booster Dose Study Results

- Factors significant for the anti-HBs ≥ 10 mIU 6-9 years post boost:
 - Pre-boost anti-HBs level
 - Response to booster dose at 2 and 4 weeks
- GMT Pre and Post booster dose
 - GMT pre-booster dose was 6.6
 - GMT was 353.9 4-6 weeks post boost
 - GMT 6-9 years post booster dose was 6.9

Hepatitis B Antibody Levels Pre- and Post-Vaccine Booster, by Initial Vaccine Series



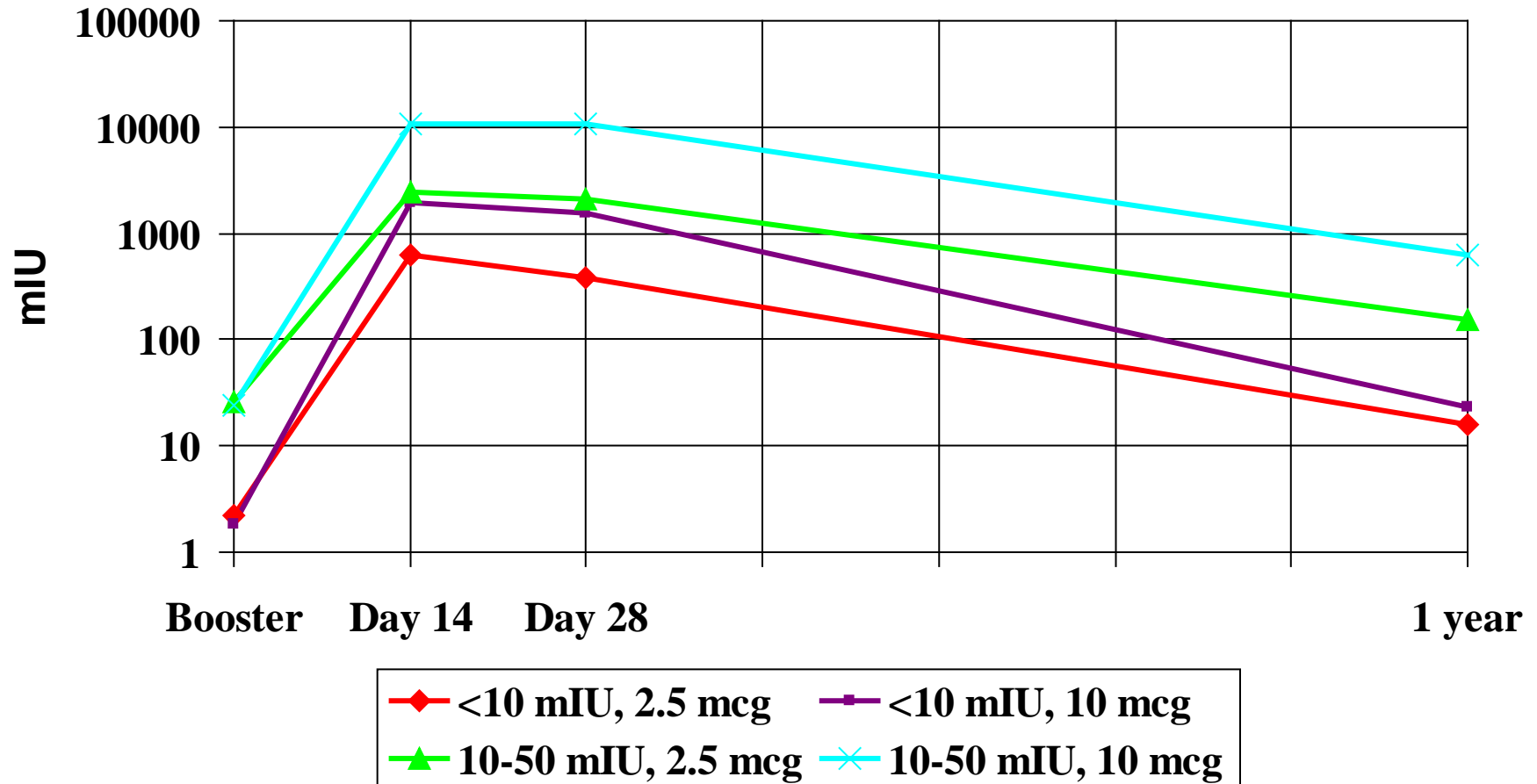
Hepatitis B Immunity Pre- and Post-Vaccine Booster, by Initial Vaccine Series



Anti-HBs Falls Rapidly After Booster Dose

- Two other Alaska studies:
 - Vax Demo 22
 - Only 41% had anti-HBs > 10mIU 1 year post boost
 - GMC fell from 87 at 2 weeks to 8 at 1 year
 - Health Care Worker (HCW) Booster Dose Study
 - Rapid fall of GMC 1 year post booster dose

Anti-HBs levels following a booster dose of hepatitis B vaccine in HCW



Conclusions Regarding Long-term Efficacy of Hepatitis B Vaccine

- Hepatitis B protects completely against acute symptomatic HBV and chronic HBV
 - Up to 22 years in those immunized as children and adults including HCW; 30 year study pending
 - Up to 15 years in those immunized as infants

Conclusions Continued

- Protection may wane over time as seen by failure to respond to a booster dose
 - 7% immunized as children or adults by 22 years
 - Up to 40% immunized as infants by 15 years
 - However T Helper and memory cells likely remain longer and could protect against acute or chronic HBV disease.
- Response to booster dose falls rapidly even by 1 year
 - Following response to booster dose may not be an adequate method to determine long-term immunity