The Impact of Hepatitis A and B Vaccination in Alaska

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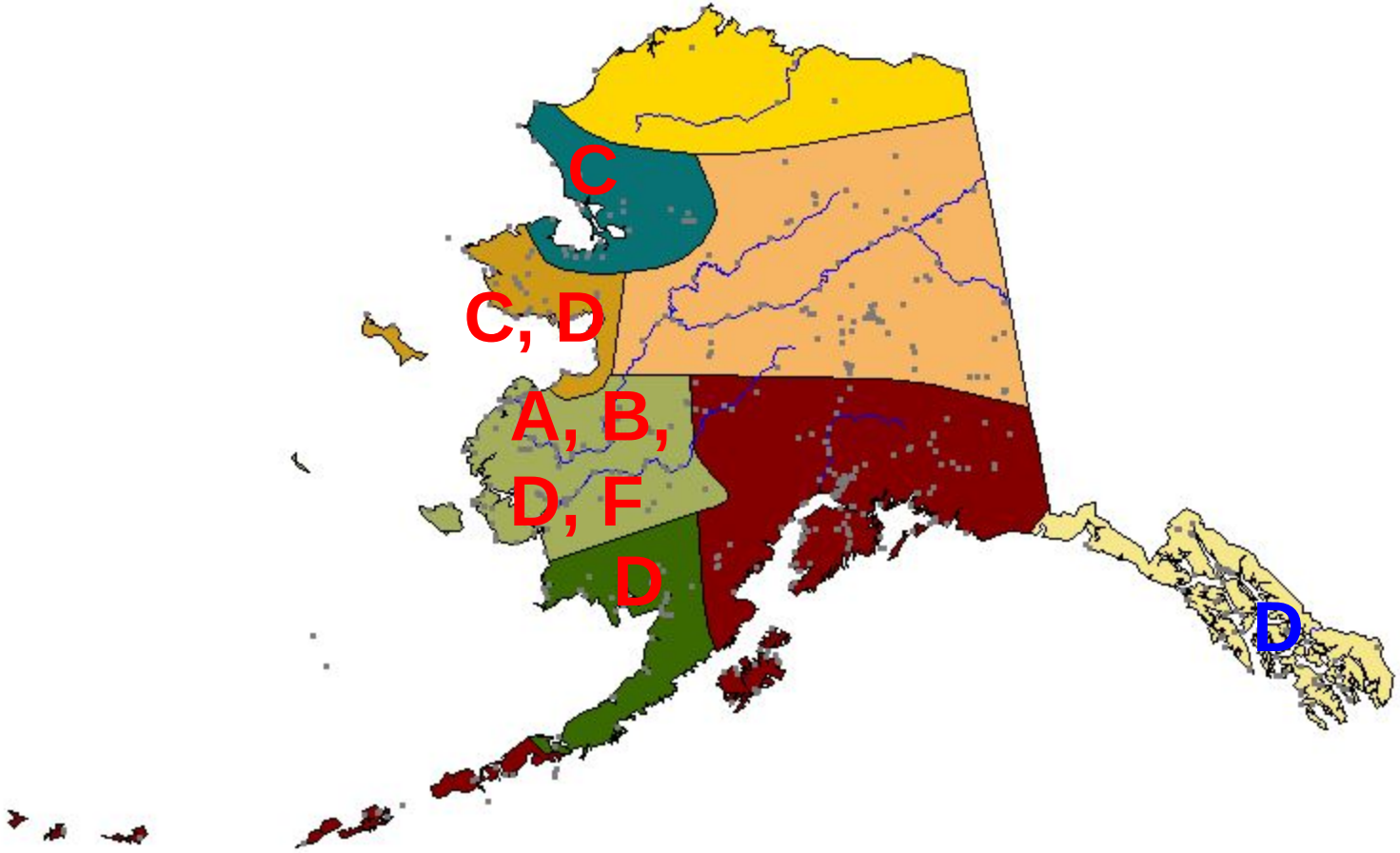
Historical Background

- Alaska Natives (AN) had the highest prevalence and incidence rate of hepatitis B virus (HBV) of any non immigrant group in US
  - Incidence of HCC highest in AN in US
- The highest rates of acute hepatitis A virus in US in most years up to 1995 was found in Alaska

Geographic Distribution of HBV Genotypes in Alaska Natives



Hepatitis B in Alaska Natives

- 1972-73: High incidence acute hepatitis B
- 1973-1974: Serosurvey found prevalence of HBsAg in 12 villages in Southwest AK 6.4% (0-20.1%)[1]
- 1974-1978: Incidence study 1280 seronegative persons: 14.8% HBV[2]
  - 29% infected < 5 years became chronic carriers
  - Transmission mainly horizontal from child to child probably through open cuts and scratches
  - HBsAg was found all over environmental surfaces (school lunchroom table tops, homes of carriers)

[1]Schreeder Am J Epidemiol 1983; 118:543-9

[2]McMahon JID 1985; 151:599-603

Intervention to Control HBV in Alaska: Questions in 1980

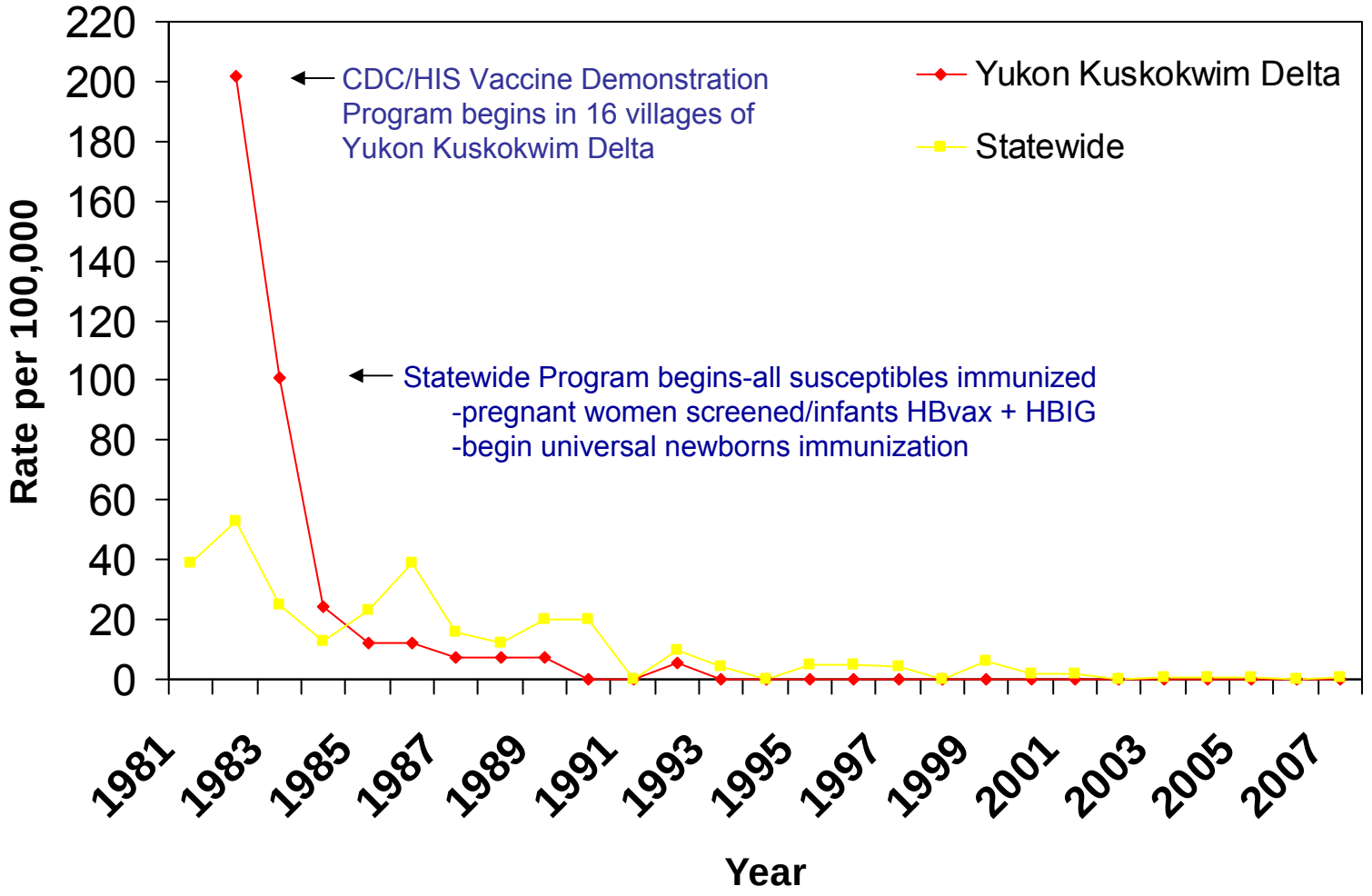
- Can we halt the spread of HBV with the new HBV vaccine?
- If so, how long will protection last?
- What about those chronically infected who would not benefit by vaccination?
  - Can we detect hepatocellular carcinoma early enough to resect
  - Will we eventually be able to treat chronic HBV with antiviral therapy

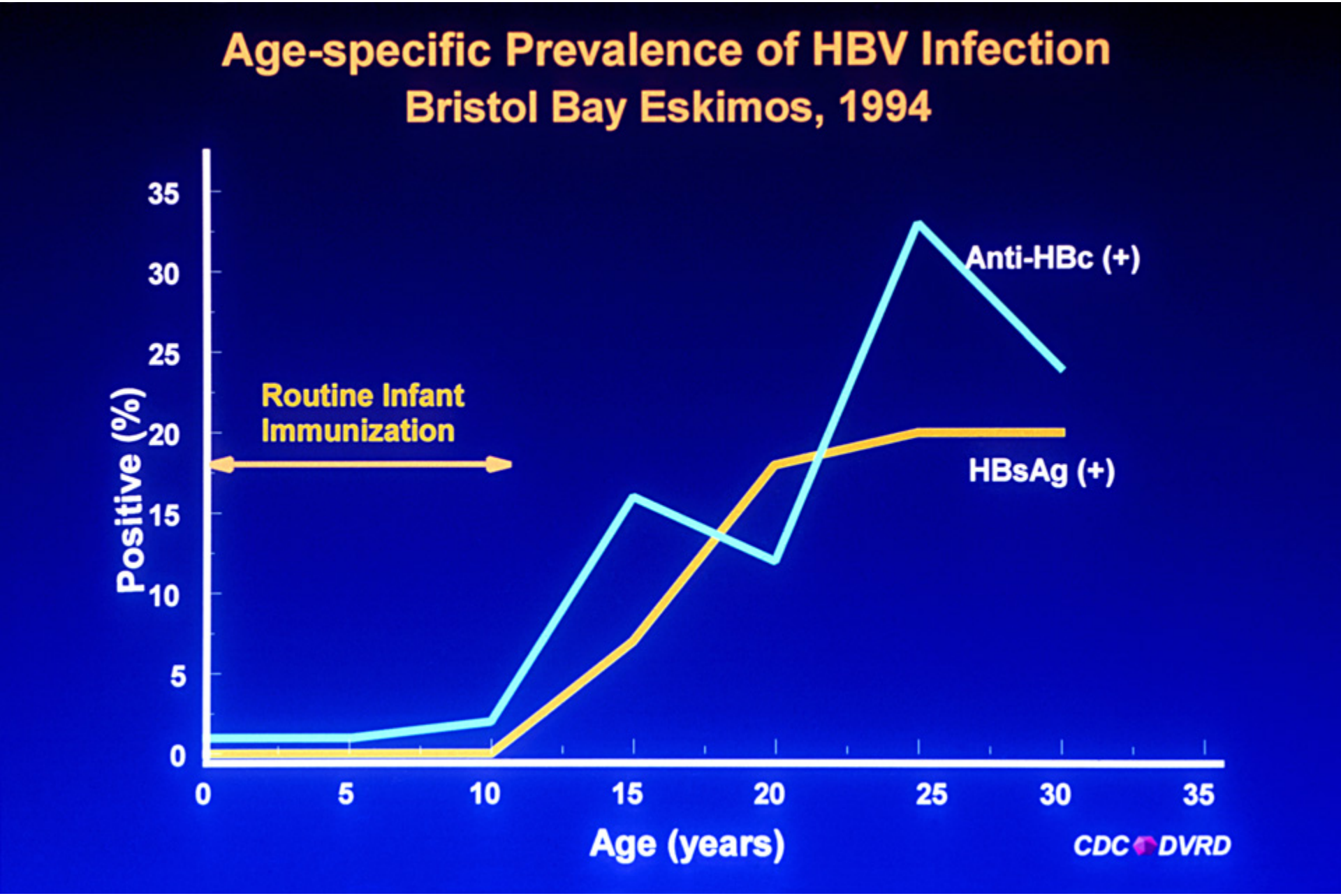
Hepatitis B Vaccination in Alaska

- 1981-82: Hepatitis B vaccine demonstration project in Southwest Alaska (Am J Epidemiol 1985;121:914-923)
- AN Hepatitis B Control Program: A collaboration between IHS, CDC, AN Health Corporations and State of Alaska with Congressional Funding
- 1983-87: 53,000 Alaska Natives screened and 40,000 susceptible were vaccinated
- 1984: Hepatitis B vaccination of all infants

Lancet, 1987; 330:1134-1136

Incidence Symptomatic Hepatitis B in AK Natives 1981- 2003





J Infect Dis 2000;181:413-418

How Long Does Protection after Hepatitis B Vaccine Last?

- How fast does anti-HBs decay
- Do break through HBV infections occur?
- What are the implications of breakthrough infections?
- In persons who lose anti-HBs, can humeral immunity be demonstrated
  - Anamnestic response to booster dose
- Does cellular immunity last longest?

Long-Term Immunogenicity & Efficacy: Children & Adults

- Alaska HBV Vaccine Demonstration Project: 1530 children and adults immunized in1981
  - Followed yearly for 11 years and at year 15
  - No booster given at 1-11 and 15 years
  - % with anti-HBs levels > 10 mIU/ml
    - 5 years: 81% (JAMA 1989;261:2362-6)
    - 7 years: 74% (Arch Int Med 1991;151:1634-6)
    - 15 years, 66% (Ann Int Med;2005;142:333-41)
- Test all participants for anti-HBs, HBsAg, anti-HBc
  - Sequence HBV DNA if HBsAg or anti-HBc+

Long-Term Immunogenicity & Efficacy: Alaska Study at 15 years

- No chronic carriers or acute symptomatic HBV cases were identified
- Anti-HBs GMC decreased from mean concentration of 822 mIU/ml to 27 mIU/ml
- 23 HBV breakthrough infections defined by appearance of anti-HBc
- Significantly more breakthrough infections in non responders compared to responders
- 6 were transiently HBV DNA positive, 4 of whom had HBV surface mutants and one transiently had 145R escape mutant

McMahon Ann Int Med 2005;142:333-41

Alaska HBV Vaccine Demonstration Project: 22 Year Follow-Up

- Residents of 7 villages, 9 villages not studied
- % with anti-HBs levels > 10 mIU/ml
  - 5 years: 81%
  - 7 years: 74%
  - 15 years, 66%
  - 22 years 59%
- Booster dose Recombivax® 5 mcg given to those who with anti-HBs <10 mIU/mL:

Vax Demo 22: Study Design

- Blood Draw/Boost schedule
  - Day 0: Pre booster draw/booster dose
  - Day 10-14: Post booster blood draw
  - Day 30-60 Post booster blood draw
- Booster (anamnestic) response at 2 weeks:
  - 4-fold anti-HBs increase, ***or***
  - Increase to > 10mIU/mL

Vax Demo 22: Preliminary Results in Persons Who Responded to Initial Series

- 5 persons anti-HBc positive (all previously identified, all HBV DNA negative
- 184 (41%) with anti-HBs <10 mIU/mL
  - 155 received booster and follow up
    - 113/147 (77%) with boost at 10-14 days
    - 125/155 (81%) with boost at 30-60 days
- Overall, 94% (95% CI: 91.0% – 95.6%) had evidence of immunity: either boosted at 10-14 days **or** had anti-HBs ≥10 mIU/mL at 22 years

How Long Will Protection from HBV Vaccine Last when Given at Birth?

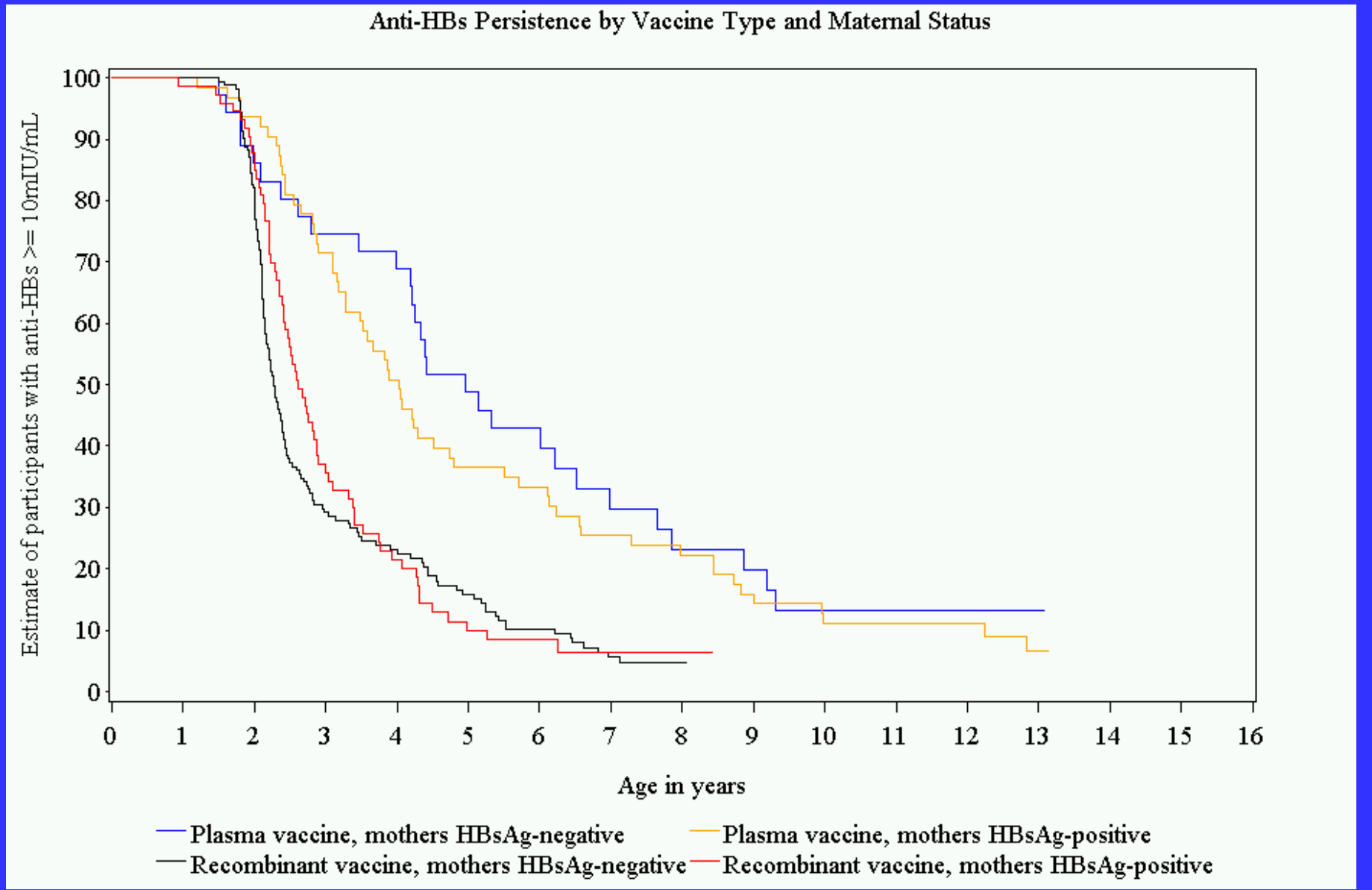
- Few studies beyond 10 years
- Infants of HBsAg+ moms and/or those living in an endemic environment have longer persistence of anti-HBs
- Demonstration of long-term immunity
  - Persistence of anti-HBs
  - Response to booster dose

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

- 334 children immunized starting at birth with documented anti-HBs response ≥10 mIU/ml followed for up to 15 years (median 10 years)
- At 5 years 49% who received plasma and only 6% who received recombinant vaccine had anti-HBs levels ≥ 10mIU/ml
- At 10 years 21% who received plasma and 3% recombinant vaccine had anti-HBs ≥ 10 mIU/ml

Ped Infect Dis J 2005;24:786-92

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



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

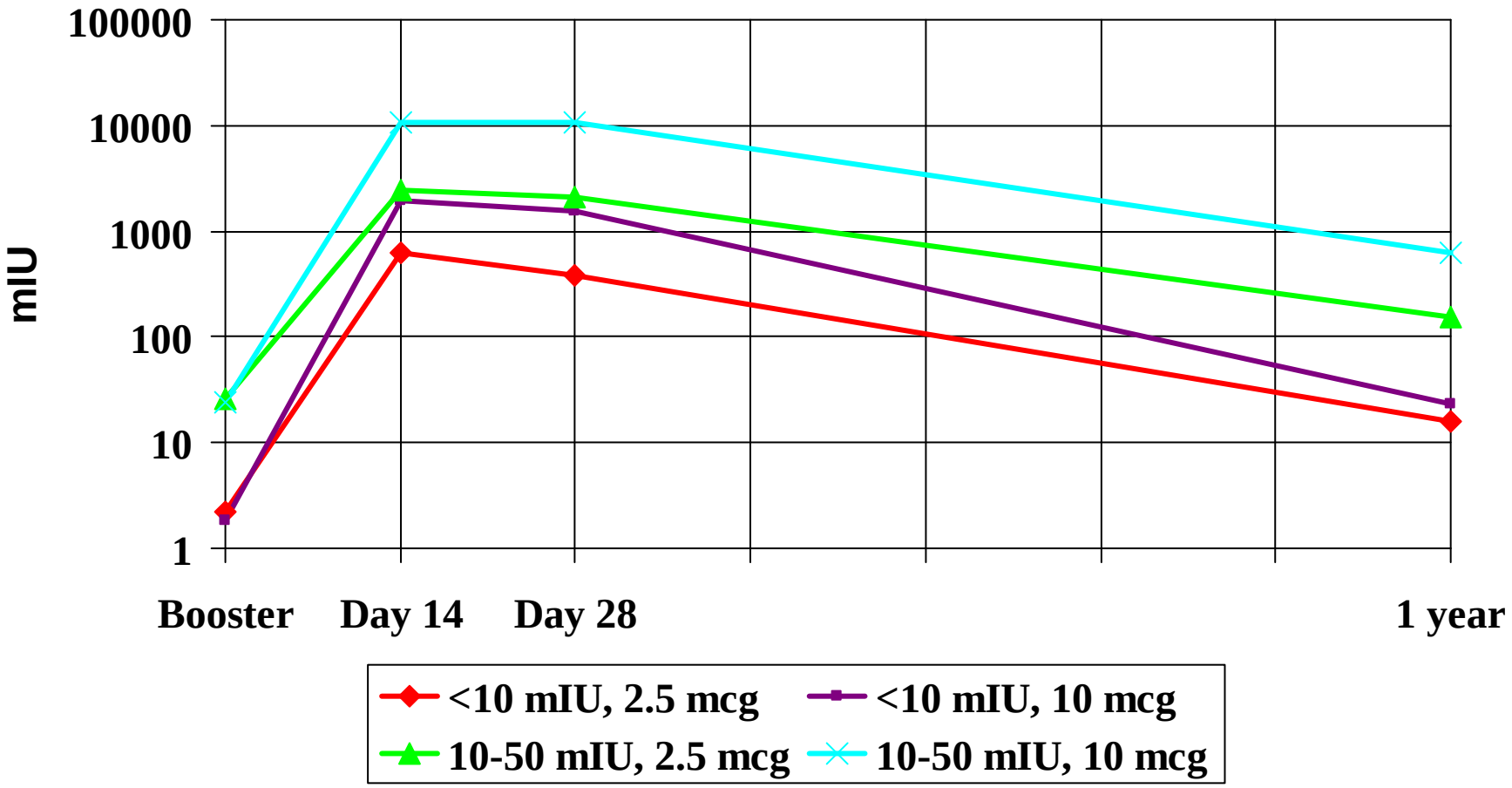
Age at Boost Moms HBV neg	% anti-HBs >10	No. Boosted	No. (%) response
5 years*	12.5%	134	90%
5-7 years**	29%	158	99%
7.5 years*	0%	35	91%
10-15 years**	5%	138	88%
15 years^	0%	35	51%

*Peds Infect Dis 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%

Anti-HBs levels following a booster dose of hepatitis B vaccine in HCW 3 to 13 Years after Initial Vaccination



Williams Vaccine 2001;19:4081-85

Long-Term Protection with Hepatitis B Vaccine: Conclusions

- Hepatitis B Vaccine provides long-term protection
- Immunity persists after loss of anti-HBs
- Documented protection:
  - Lasts 15-18 years in infants
  - Up to 13 years in Health Care Workers
  - 22 years in children and adults
- Lifelong protection is possible
- No evidence “vaccine escape mutants” are a threat
- Continued follow-up needed to determine duration of protection
- Booster doses NOT currently recommended

Future Studies on Long-Term Efficacy of Hepatitis B Vaccine In Alaska

- F/u up of all remaining participants in 1981 immunogenicity study 30 years after vaccination: Estimated number is ~900
- F/u up of children who received a booster dose of hepatitis B vaccine at school entry or adolescence to determine anti-HBs persistence after booster dose

Importance of Alaska Long-term Hepatitis B Vaccine Studies

- 1981 immunogenicity study is by far the largest and longest f/u study of HBV vaccine in the world
- This study is crucial to ACIP and other national/international organizations future recommendations for booster dosing in children, adults and health care workers and thus far has shown that no boosters are needed in those immunized as children over 1 year of age or adults 22 years later

Hepatitis A Story in Alaska

- 1984-1987: Study showed high rates of past hepatitis A infection*
- 1987: Large epidemic begins
- 1989: Hepatitis A vaccine trial in Alaska Native and non-Native adults and children
  - McMahon J Infect Dis 1995;171:676-9
- 1991: Hepatitis A vaccine licensed Europe
- 1993: Hepatitis A outbreak stopped by giving one dose of vaccine to 5000 people

*J Infect Dis 1993;168:1017-20

*Peach, J Infect Dis 2002;186:1081-5

Geographic Distribution of HAV Infection 1985

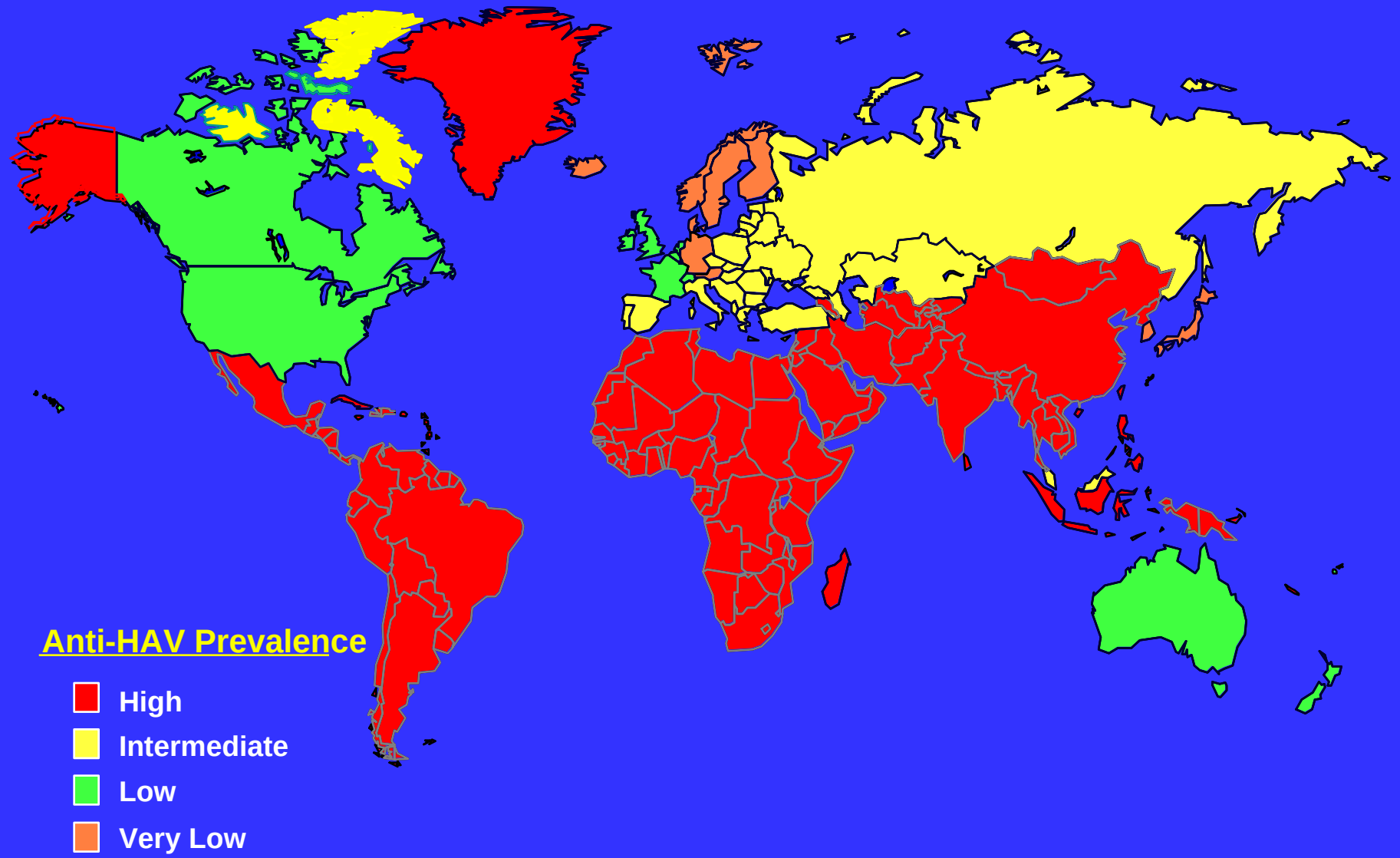
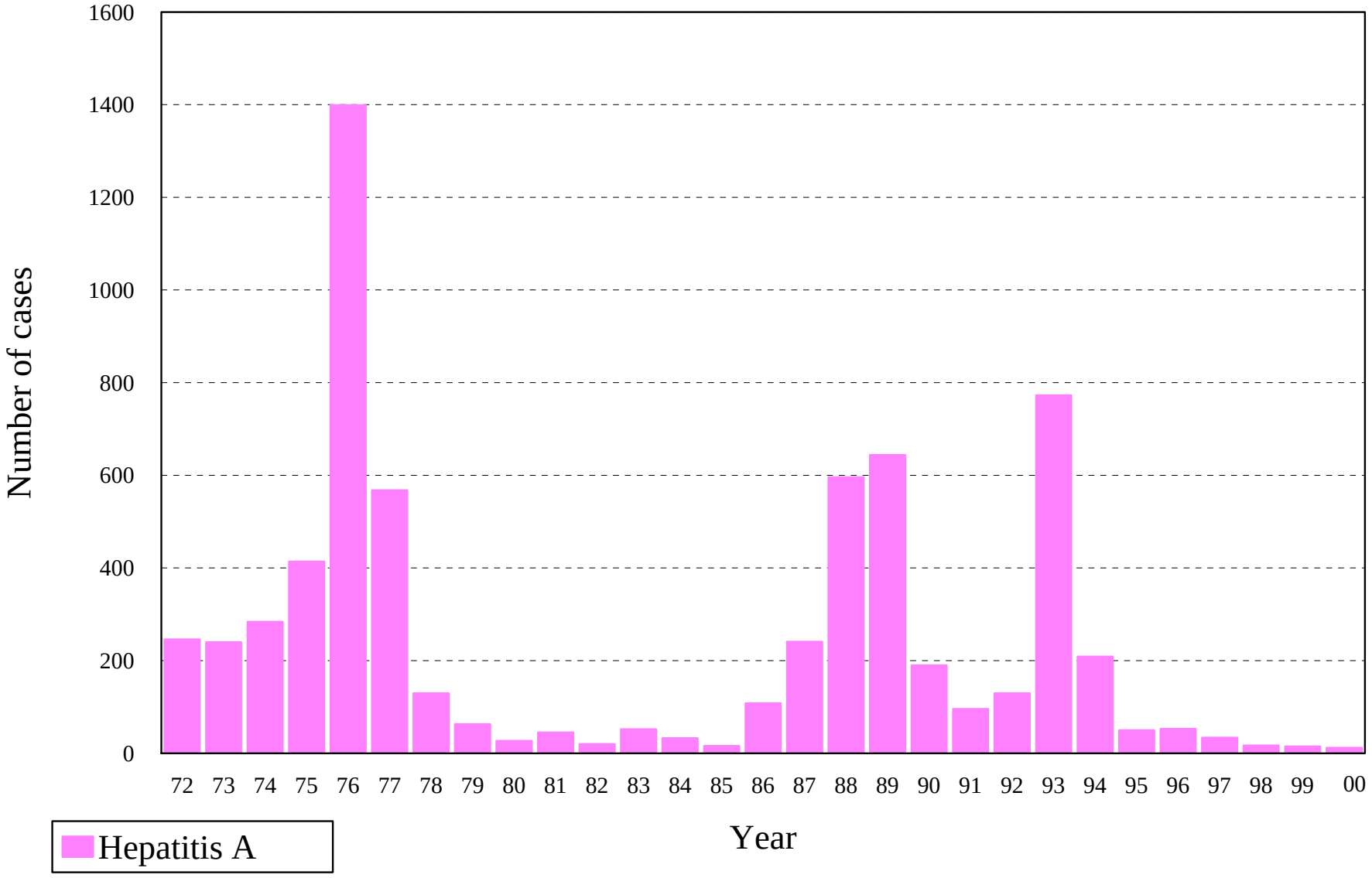
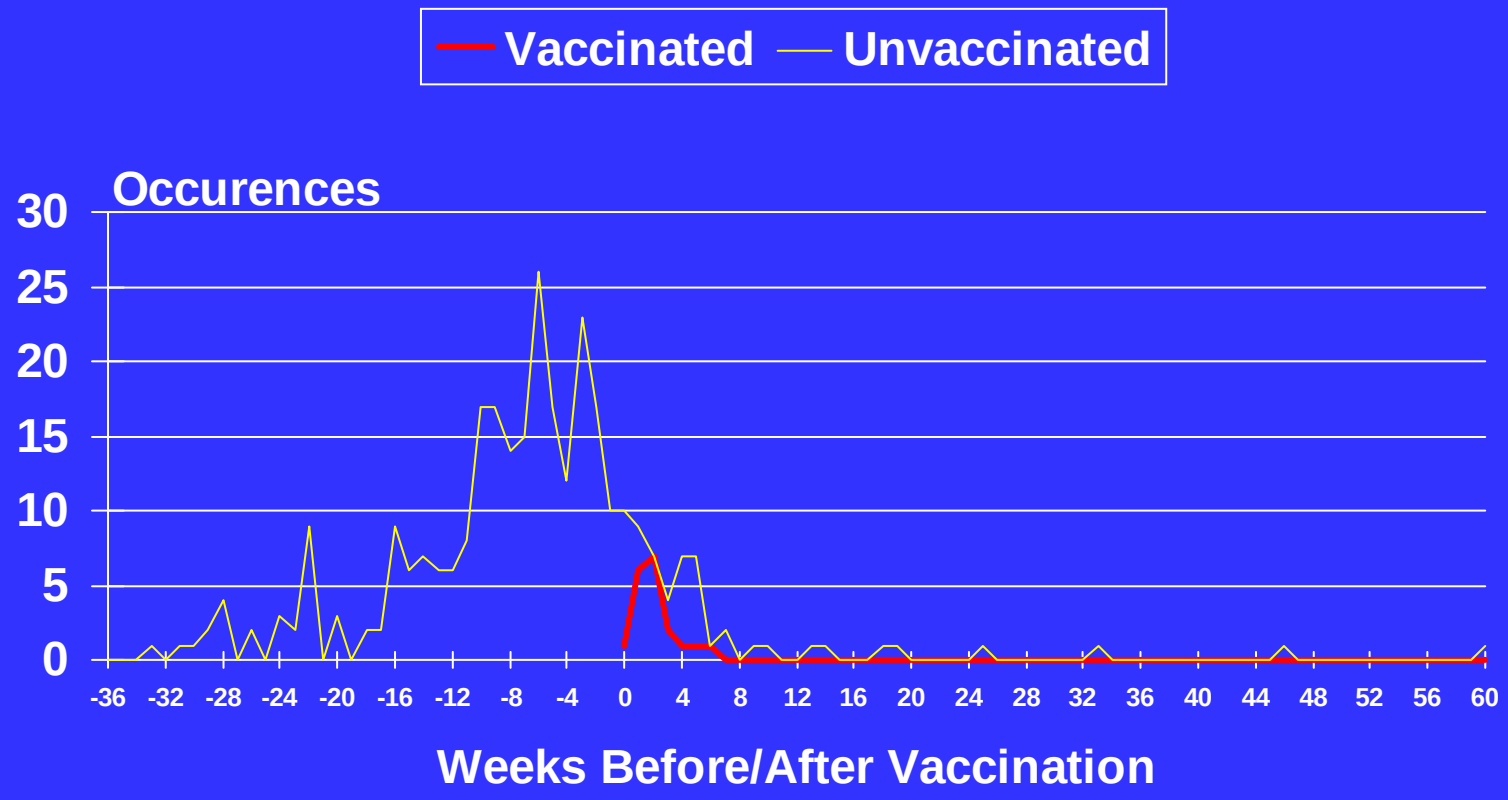


Figure 1: Reported Cases of Hepatitis A in the State of Alaska, 1957-2000



Hepatitis A Outbreak
Northwest Alaska

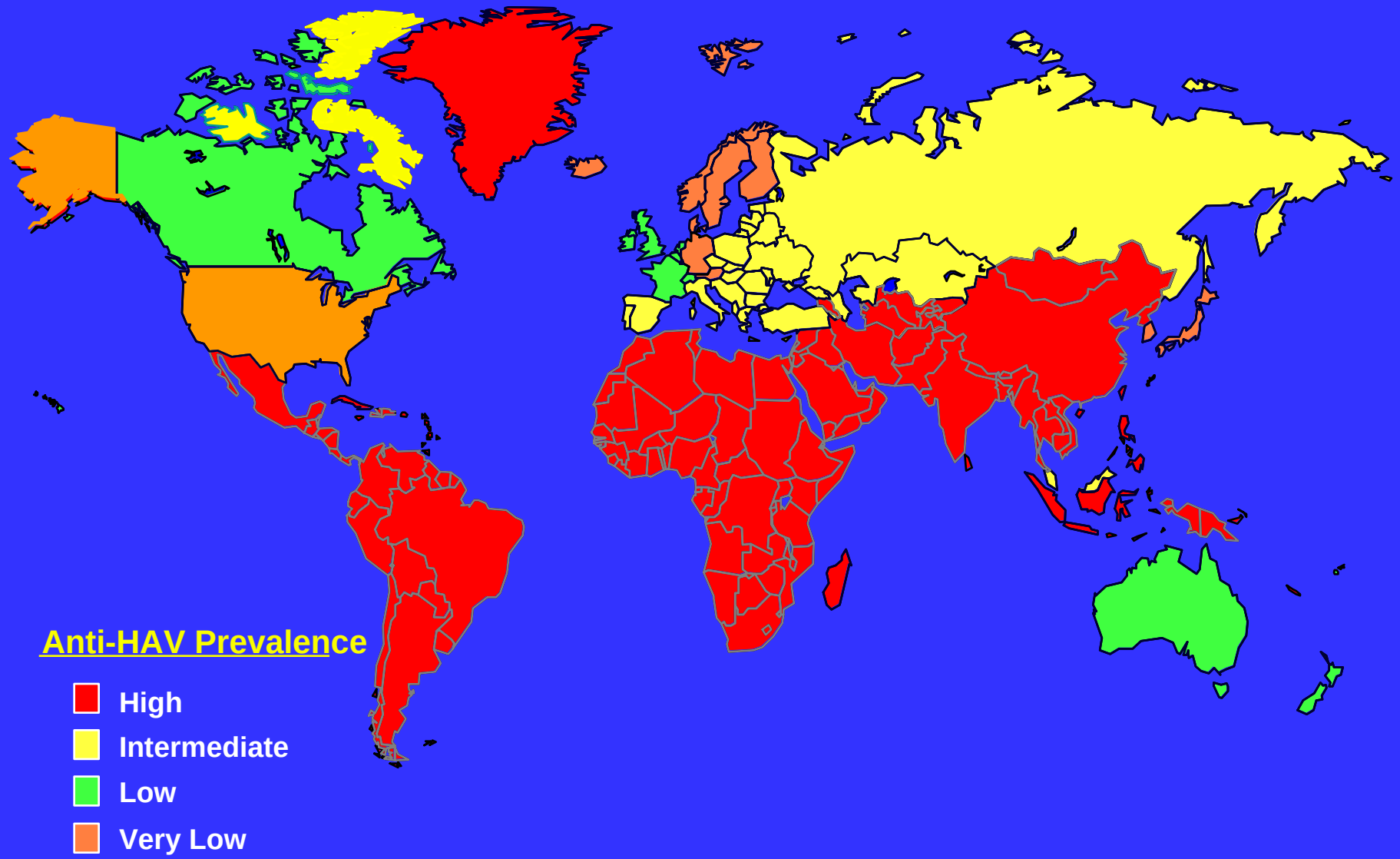


Arch Pediatr Adolesc Med 1996;150:773-9

Alaska: The First State to Offer Universal Hepatitis A Vaccine

- Beginning in 1996, Hepatitis A vaccine offered to all Native and non-Native children ages 2-18 in Alaska: 1st State in US
- Immunization results to date:
  - > 90% of all Alaskan children have been vaccinated by school entry
  - Acute hepatitis A rate falls to lowest in Nation in 2004 (< 1 case per 100,000 persons)

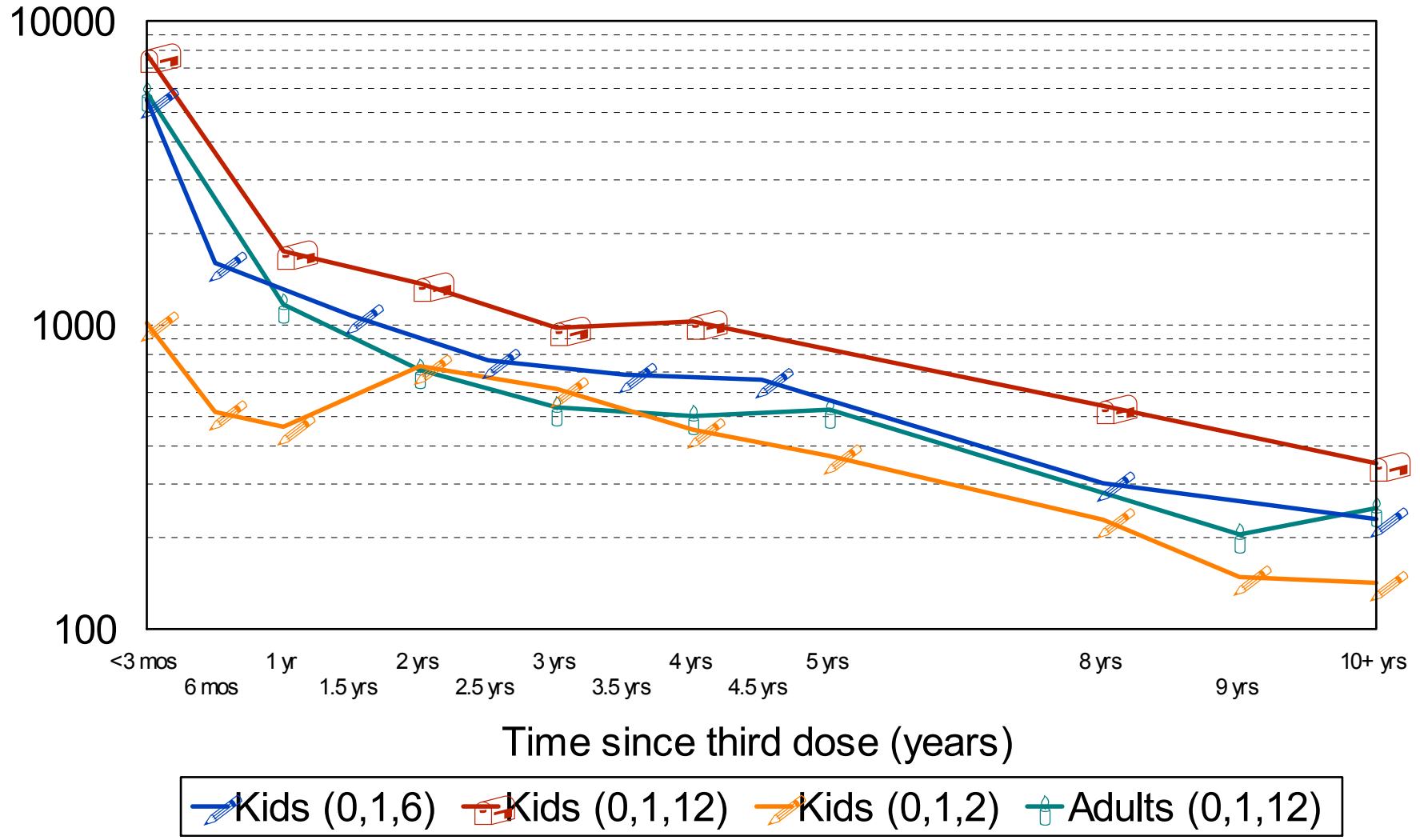
Geographic Distribution of HAV Infection 2006



Hepatitis A: Current Projects

- Long-term Immunogenicity and efficacy studies of Hepatitis A vaccine in adults, infants and children
  - 60 adults followed 10 years completed
  - 70 children, ages 3-6 f/u for 15 years
    - 100% still have anti-HAV at 10 years of age
    - Projected anti-HAV levels by modeling expected to last at least 20-30 years
  - 206 infants f/u to 10 years

Anti-HAV Declination Curve following Primary
Hepatitis A Vaccination, according to Vaccination Schedule, Alaska



Alaska Hepatitis A Infant Study

- Sites: ANMC & Anchorage Neighborhood Health Center
- Randomized trial: 2 dose hepatitis A vaccine: infants stratified by Mothers anti-HAV status
  - Group 1: Vaccine 6 and 12 months of age
  - Group 2: Vaccine 12 and 18 months of age
  - Group 3: Vaccine 18 and 24 months of age
- Response other childhood vaccines to detect measured to detect any interference from Hep A

Peds Infect Dis J 2007;26:116-22

Anti-HAV Concentrations at 7 and 12 Months After First Hepatitis A Vaccine Dose, by Group, HAVIIS

	7 Months after Vaccine				12 Months after Vaccine			
Group	N	% Positive[1]	GMC[2]	95% CI[3]	N	% Positive[1]	GMC[2]	95%
1N	43	100	2182	1539 – 3095	44	100	741	540 – 1017
1P	35	94	809	503 – 1299	33	94	226	141 – 364
1X	18	100	2454	1452 – 4146	15	100	817	508 – 1313
2N	38	100	3166	2413 – 4156	42	100	882	673 – 1157
2P	33	100	2296	1719 – 3068	29	100	698	499 – 976
3N	43	100	3199	2475 – 4136	38	100	915	684 – 1223
3P	32	100	2791	2102 - 3706	28	100	870	604 - 1252

[1] Seropositivity based on anti-HAV concentration of 33 mIU/mL

[2] Geometric Mean Concentration (mIU/mL). If anti-HAV<33 mIU/mL then assigned value of 15 mIU/mL for GMC calculation.

[3] 95% Confidence Interval

Long-Term Hepatitis A Vaccine in Infants

- 206 infants f/u to 10 years
- Plan to test sample of 7-year f/u bloods.
- If anti-HAV is still present in > 90%, will wait until 10-year sample complete (2008) before testing entire cohort.
- If 10-year results show good immunogenicity, will continue study to 15 years and then test all participants samples again to decide on further f/u beyond 15 years

Importance on Alaska Hepatitis A Studies

- Largest cohort of participants immunized as children with longest f/u period in world
- Largest cohort of participants immunized as infants with longest f/u period in world
- Studies are crucial to evaluate long-term effectiveness of US strategy to immunize all children between 1 and 18 years

Conclusions

- Alaska has gone from the highest rates of acute hepatitis A statewide and B in Alaska Natives in the US to the lowest rate of acute hepatitis A and B in the World (<1/100,000)
- Long-term protection from these vaccines lasts for at least 15-22 years for hepatitis B and are projected to last for at least 20-30 years for hepatitis A