Viral Hepatitis Update: Screening, Vaccination, and Treatment

Alaska Maternal Child Health & Immunization Conference

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Hepatitis A Virus (HAV) Vaccine

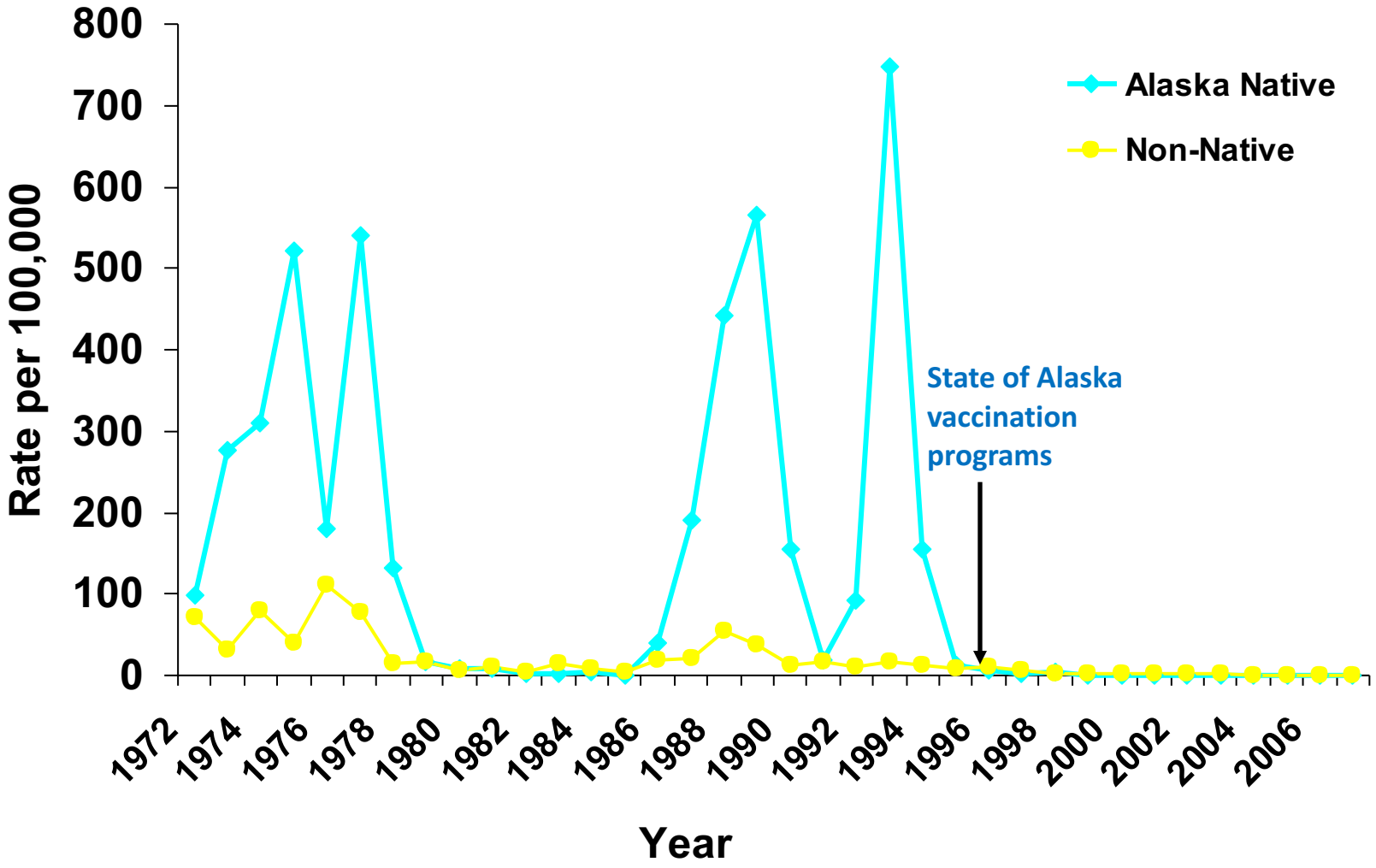
Background

- During 1980—1995
  - ~271,000 HAV infections/year in United States
  - 22,000—36,000 symptomatic cases/year
- Inactivated HAV vaccine initially licensed in 1995
  - Supported by prelicensure studies done at ANTHC
  - Not approved for children aged <2 years because of concern that maternal anti-HAV antibodies would interfere with vaccine immunogenicity
- HAV vaccine licensed for children aged 12—23 months in 2005
  - Supported by postlicensure studies done at ANTHC

ACIP HAV Vaccination Policy – Incremental Implementation

- First recommendation targeted (1996)
  - Children living in communities with the highest disease rates (a population that included AN children)
  - Persons at increased risk for HAV infection (e.g., travelers) or adverse outcomes (e.g., persons with chronic liver disease)
- Recommendation expanded to include children living in communities where HAV infection rates were above the national average (1999)
- Recommendation for routine vaccination of all children nationally (2006)
  - Goal: End transmission of HAV within the United States

Rates of HAV Infection --- Alaska, 1972-2006



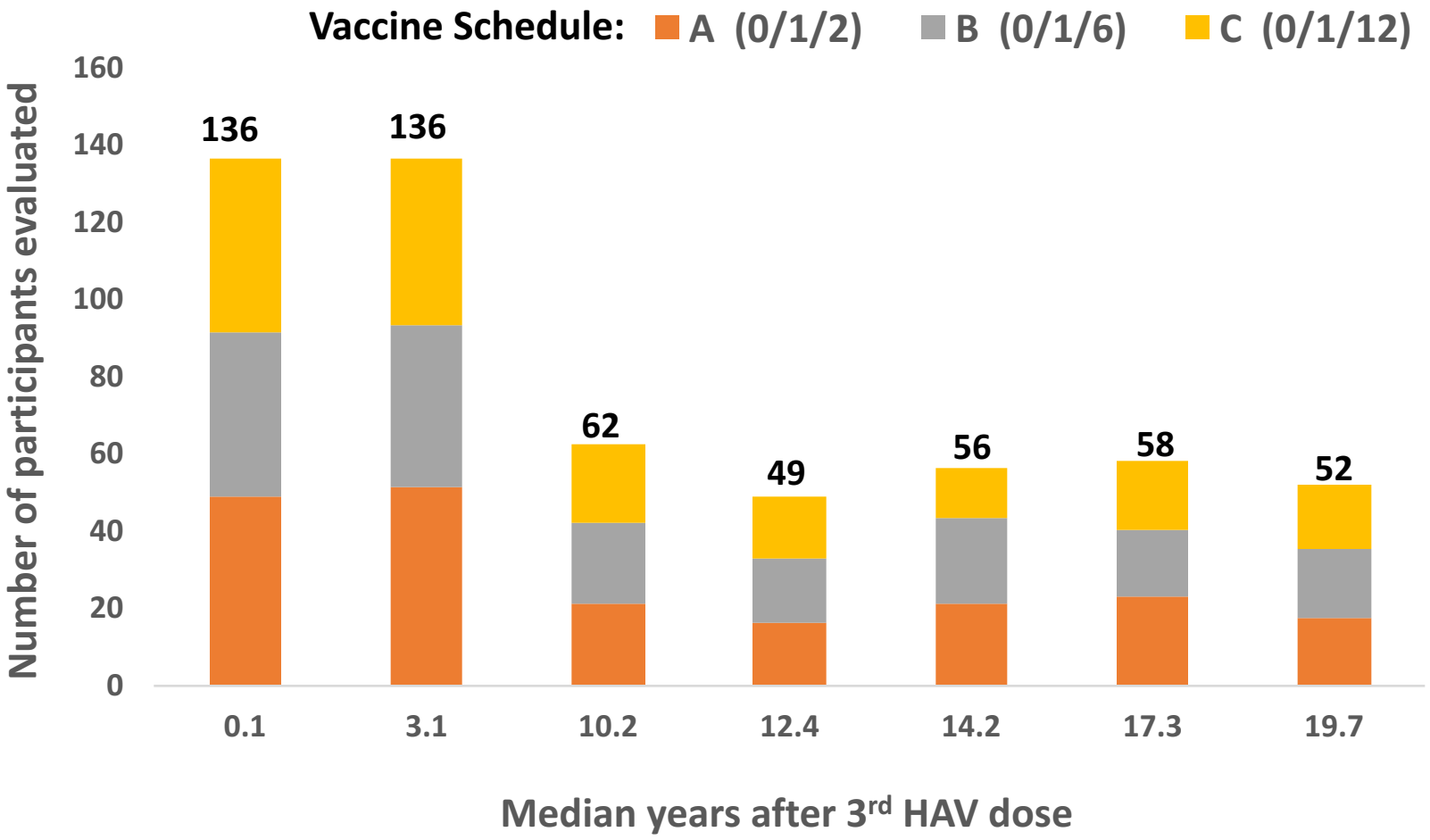
ANTHC HAV Vaccine Studies

- Objective: To evaluate duration of protection from HAV vaccine
- 2 long-term randomized studies
  - Prelicensure study in children aged 3—6 years
  - Postlicensure study in infants and children aged <2 years
- Longest followed cohorts of HAV immunized children in the world

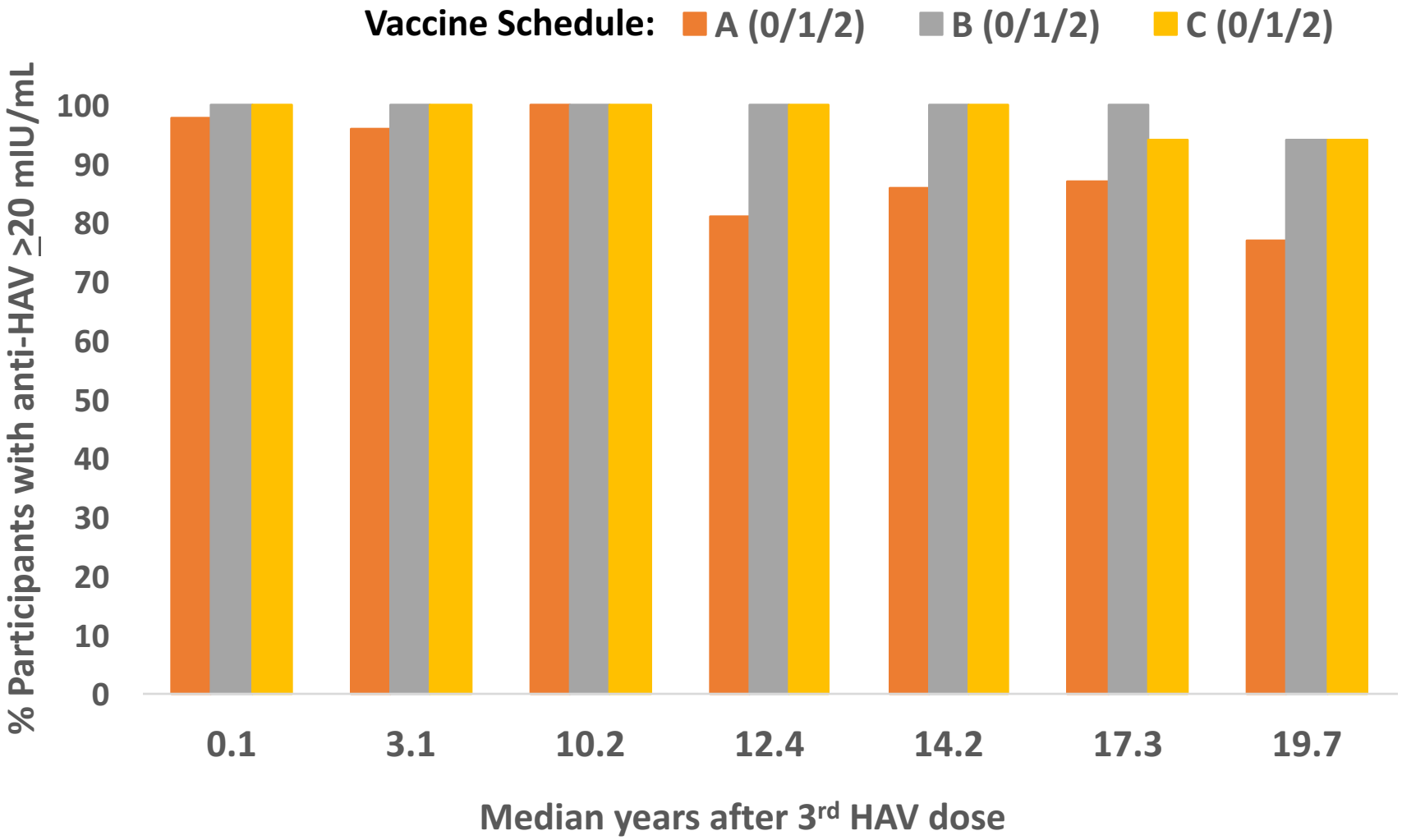
Immunogenicity of 3-dose HAV Vaccine Schedule: 20 Years Post-Vaccination

- 144 Alaska Native children enrolled 1989-1991
- Randomized to one of three vaccination schedules (360 ELISA units/dose):
  A. 0-1-2 months
  B. 0-1-12 months
  C. 0-1-15 months
- Anti-HAV antibody levels
  - Measured by modified ELISA
  - Antibody concentration $\geq$20 mIU/mL considered protective

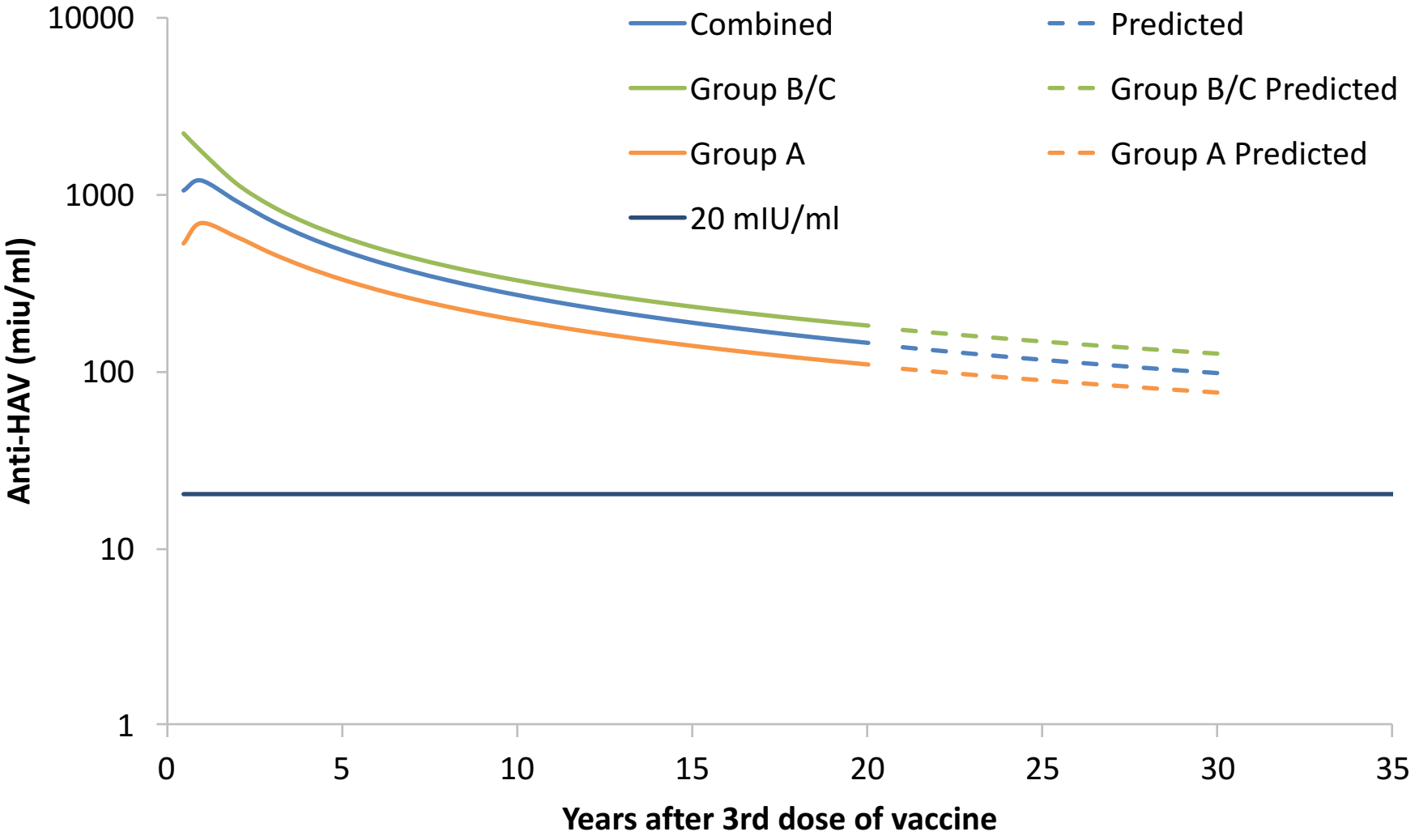
Participants Available for Evaluation Up To 20 Years Post-Vaccination



Proportion of Participants with anti-HAV ≥20 mIU/mL During Follow-Up



Predicted Duration of HAV Vaccine Protection



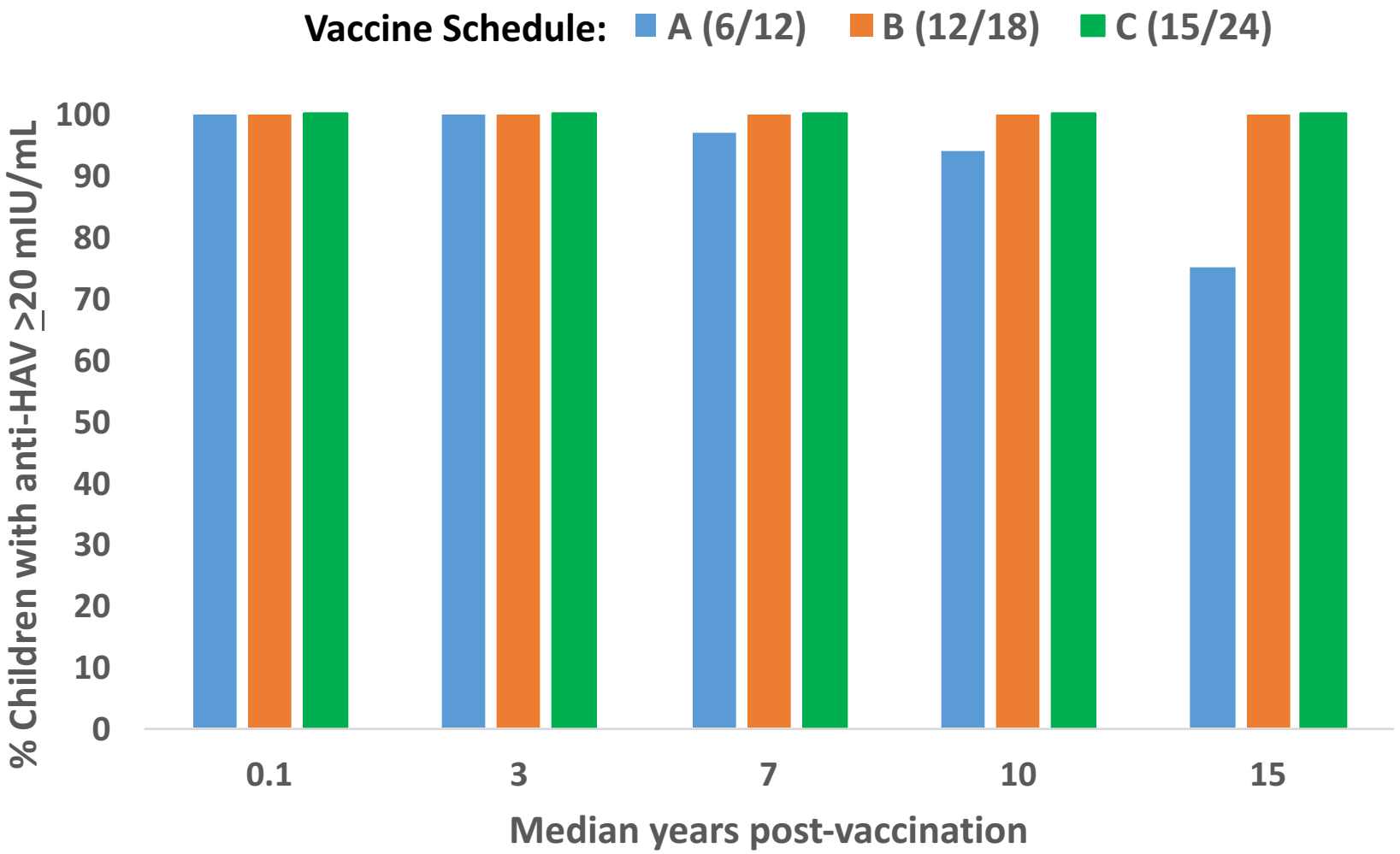
Immunogenicity of 2-dose HAV Vaccine Schedule: 15 Years Post-Vaccination

- Rationale:
  - The licensed vaccine and schedule was different from prelicensure study (2 doses of 720 ELISA units/dose rather than 3 doses of 360 ELISA units/dose)
  - Availability of vaccine in children aged <2 years would allow for inclusion into routine childhood vaccination schedule
- Objective:
  - Evaluate long-term immunogenicity of the 2-dose schedule
  - Determine optimal HAV vaccine dose schedule for infants and children born to HAV immune mothers
- 248 children randomized to 3 different 2-dose vaccine schedules and followed up to 15 years post-vaccination

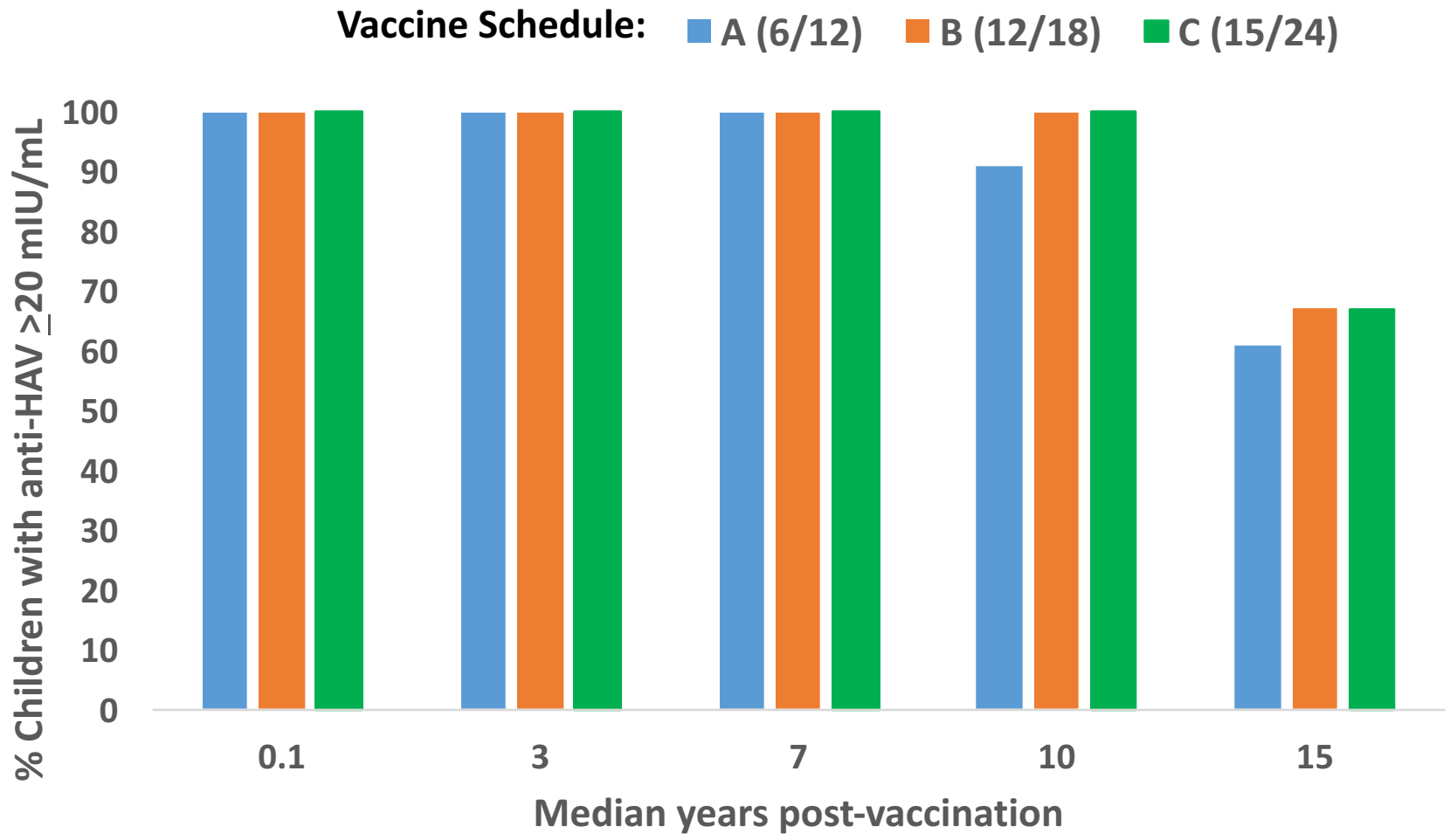
Participants Available for Evaluation Up To 15 Years Post-Vaccination

Vaccination schedule (age in months at 1st/2nd dose)	**Mother anti-HAV status**	**No. participants available for follow-up at time points post-vaccination**				
		1 month	**3 years**	**7 years**	**10 years**	**15 years**
A) 6/12	negative	40	36	33	31	20
	positive	33	35	31	22	18
B) 12/18	negative	37	35	30	21	17
	positive	17	16	14	9	9
C) 15/24	negative	36	35	34	27	19
	positive	20	20	19	12	12

Proportion Children Born to Anti-HAV **Negative** Mothers With Protective Antibody Levels



Proportion Children Born to Anti-HAV **Positive** Mothers With Protective Antibody Levels



Conclusions: Infant and Toddler HAV Study

- Protection for those vaccinated after age 1-year as currently recommended by ACIP is 100% for those whose mothers were negative for hepatitis A antibody when the child was born
- Protection for those vaccinated before age 1-year is not as robust
- Passive maternal anti-HAV may interfere with duration of antibody in offspring at 15 years of age
  - Especially maternal anti-HAV status resulted from infection
- No indication booster doses are needed for those vaccinated after 1-year of age

Hepatitis B Virus

Mother-To-Child Transmission (MTCT)

- Risk of transmission up to 90%
  - Mainly thought to occur during delivery
  - Risk not reduced by C-section
- Breastfeeding has not been associated with increased transmission
  - But recommended to feed after infant receives HBIg and first dose vaccine
  - Avoid if cracked nipples and bleeding
- Transmission risk directly related to degree of viremia
  - Transmission rarely observed if HBV DNA <20,000 IU/mL
  - Increased risk if HBeAg positive (marker of infectivity)

Testing During Pregnancy

- All pregnant women should be screened for hepatitis B surface antigen (HBsAg) – marker of HBV infection
- If HBsAg positive – test for HBeAg, ALT/AST, and HBV DNA
  - ALT/HBV DNA normal – retest 2-3months postpartum
  - ALT elevated or HBV DNA > 2,000 IU/ml – refer to a specialist for treatment evaluation
- Pregnancy in a woman with HBV infection is a reportable condition in Alaska

Interventions to Reduce MTCT

- Birth dose HBV vaccine and hepatitis B immunoglobulin (HBIg) to infant
  - Reduces MTCT by 90%
- Antiviral therapy for mother if HBeAg+ or HBV DNA >200,000 IU/ml
  - Tenofovir 300 mg daily started between weeks 28 to 32 and continued until 3 months post partum
  - In one RCT, rate of MTCT significantly lower in the tenofovir group (5% versus 18%)
  - In nonRCTs, no increase in congenital malformation rate or prematurity rate
  - Breastfeeding is not contraindicated

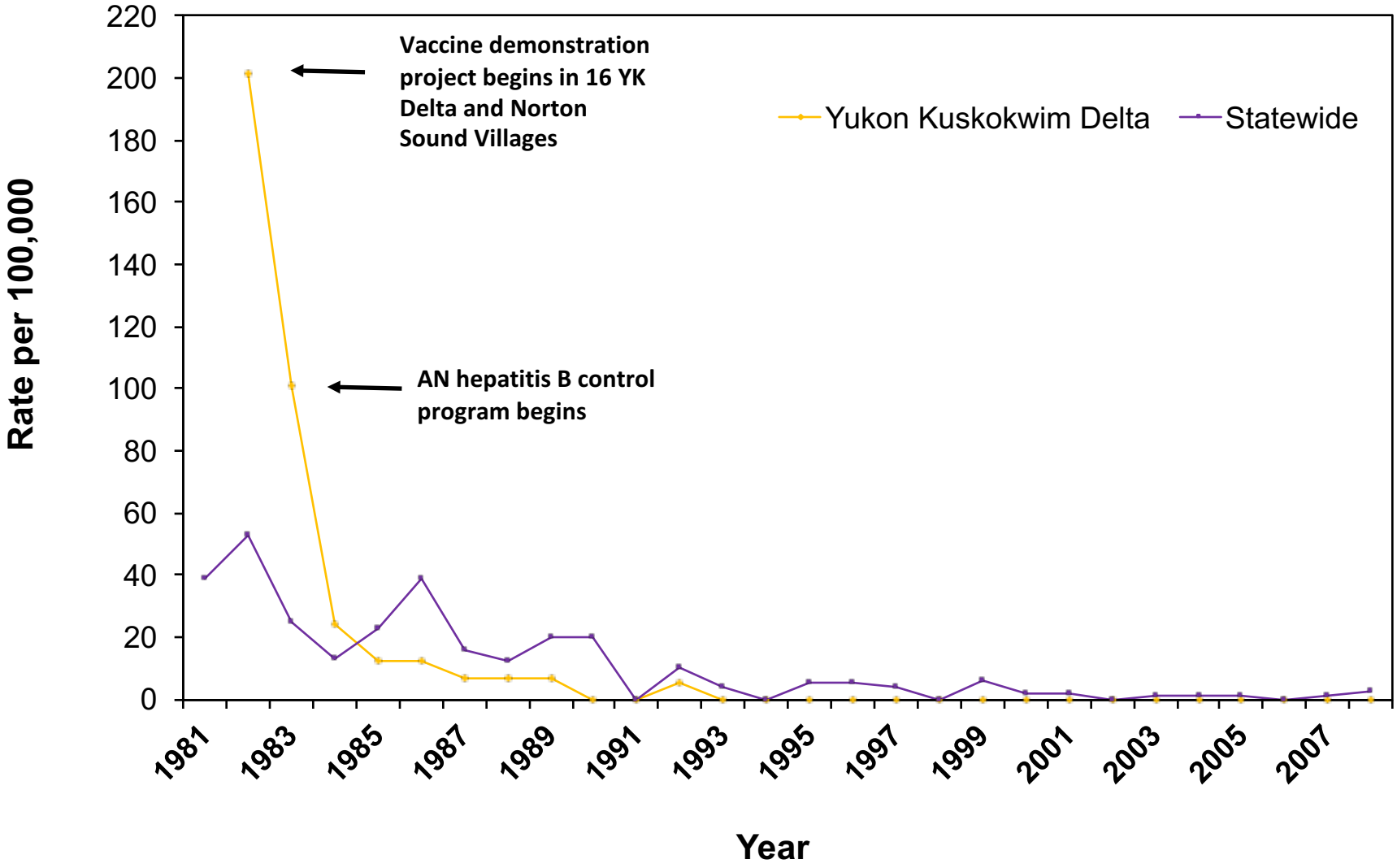
Follow-up Testing of Children Born to HBV-Infected Mothers

- Newborns should be tested for HBsAg at 1 year or HBV DNA at 3-6 months
- Antiviral therapy indicated if ALT elevated and measurable HBV DNA levels present
  - Tenofovir approved for children aged >12 years
  - Lamivudine or entecavir approved for children aged >2 years

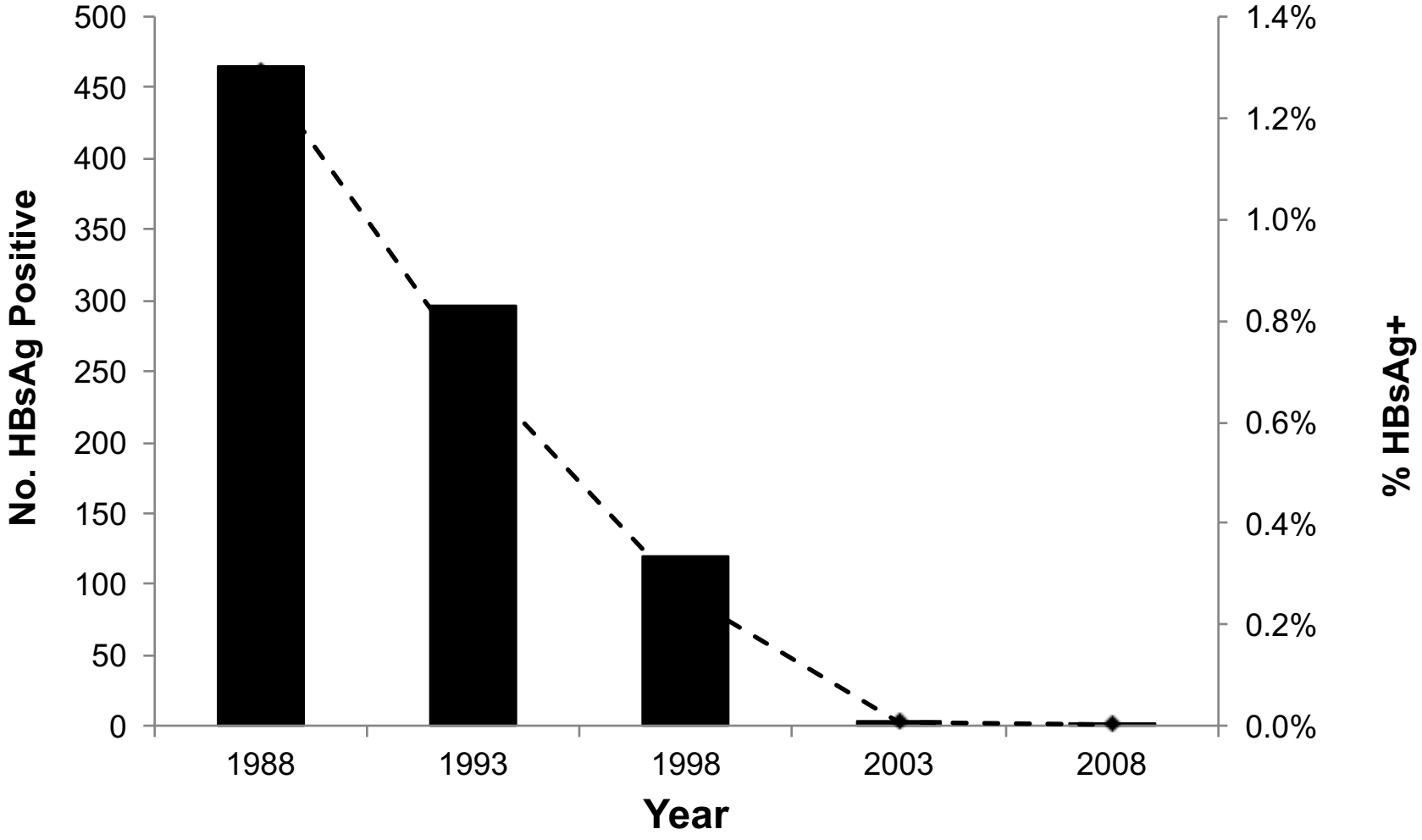
Hepatitis B Vaccination Program in Alaska

- 1981-82: ANTHC hepatitis B vaccine demonstration project in Yukon Kuskokwim Delta and Norton Sound (Vax Demo)
- 1983-87: AN Hepatitis B Control Program
  - 53,000 Alaska Natives screened
  - 40,000 susceptible were vaccinated
  - 1st place to use universal screening and vaccine
- 1984: Hepatitis B vaccination of all AN infants
  - Along with Taiwan this was 1st place in world to employ universal infant vaccination
- In 1990 all pregnant mothers at ANMC and YKHC hospitals were tested for HBsAg and infants of positive mothers given hepatitis B immune globulin

Incidence Symptomatic Hepatitis B Among Alaska Native People 1981--2008

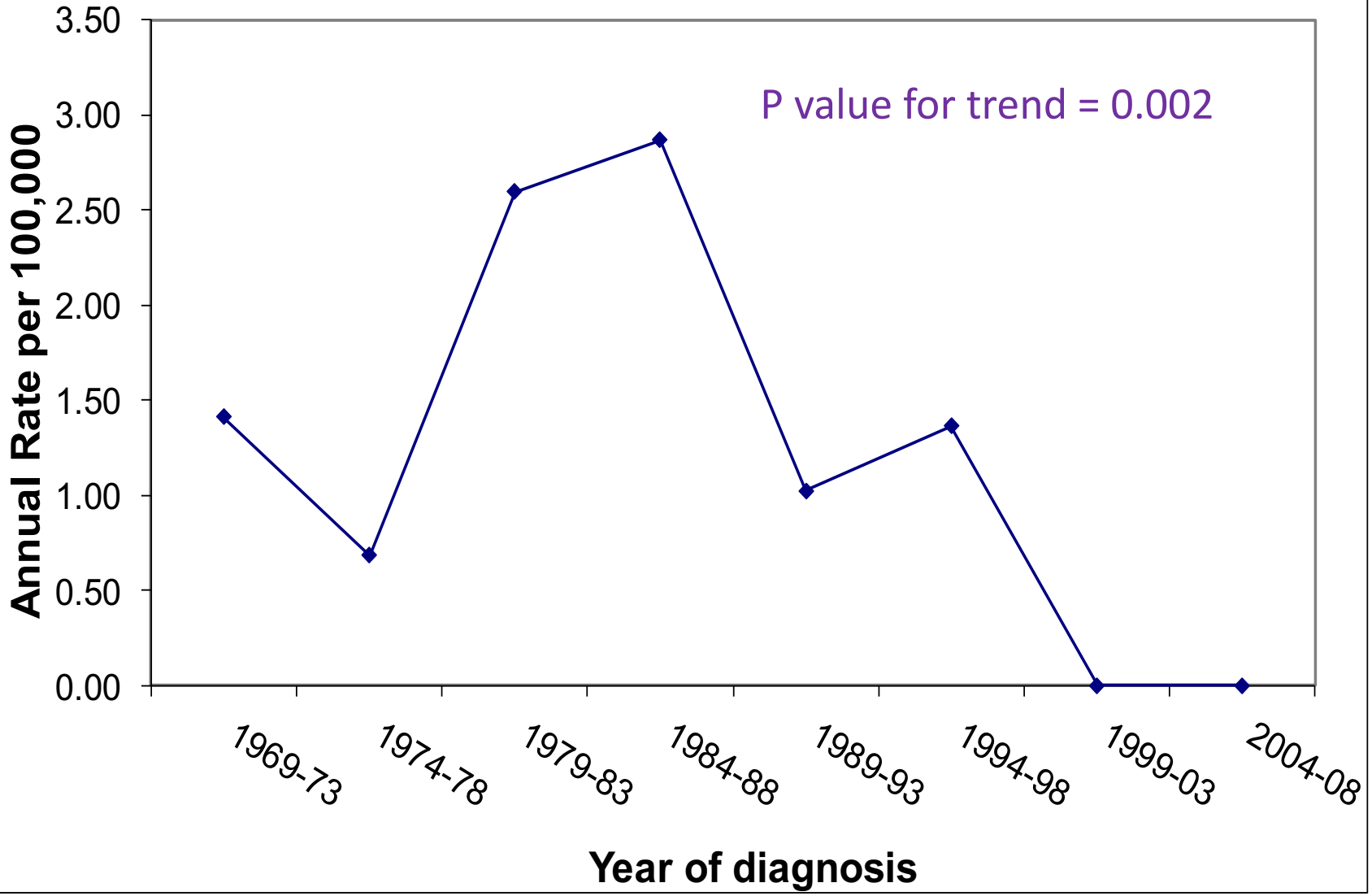


Number of HBV-Infected AN Children Aged <20 years,1988--2008



As of 2013, there are no Alaska Native children known to be HBsAg-positive

Hepatocellular Carcinoma Incidence Among AN Children Aged <20 Years



Hepatitis B Long-term Vaccine Study (Vax Demo)

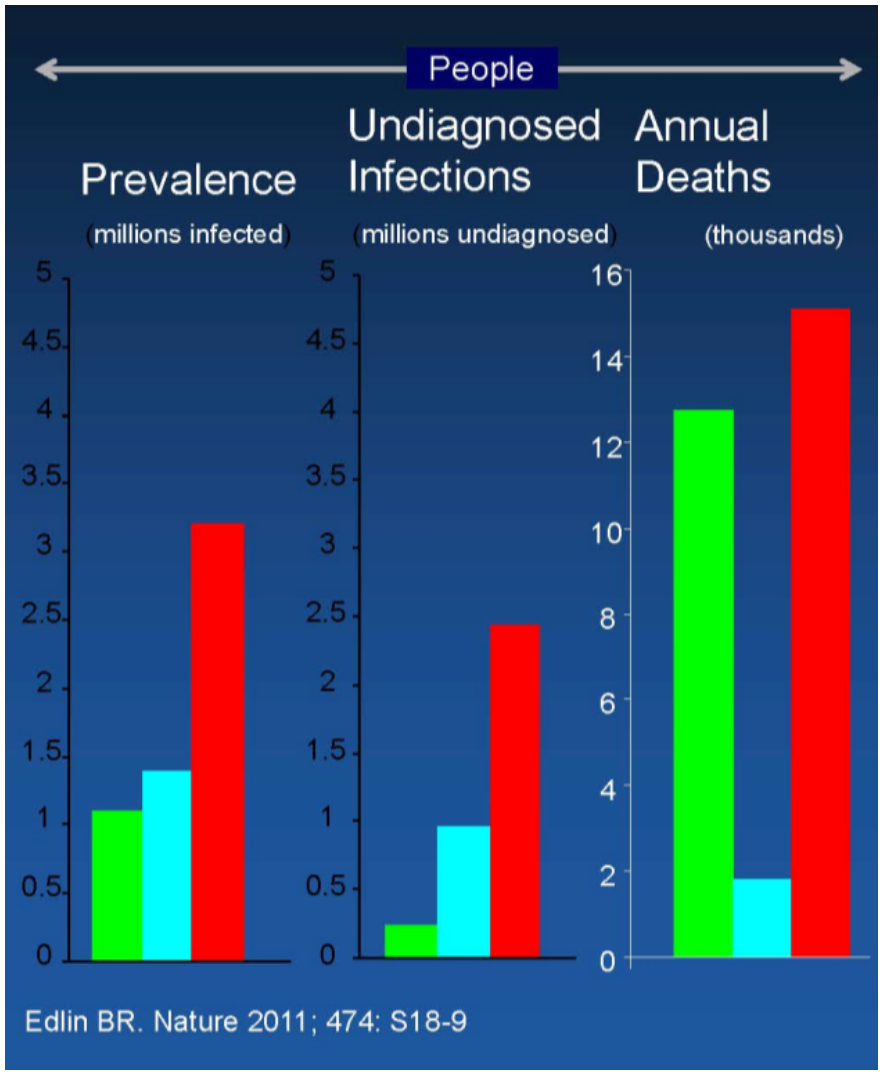
- Objective: To determine long-term immunogenicity
- 1578 AN persons ages >6 months received plasma-derived hepatitis B vaccine in 1981 followed for 30 years
  - 435 participated at 30 years
  - 50% still had protective antibody levels HBsAg (>10 mIU/mL)
  - Of those with levels <10 mIU/ml, 89% of those consenting to a booster dose responded with level >10 mIU/mL
- Overall protective efficacy was 94% (persistence of anti-HBs plus response to booster dose in those who fell below 10mIU/mL)
- Conclusion: booster doses are not needed up to 30 years post vaccination in children and adults, including health care workers

Hepatitis C Virus (HCV)

Outline

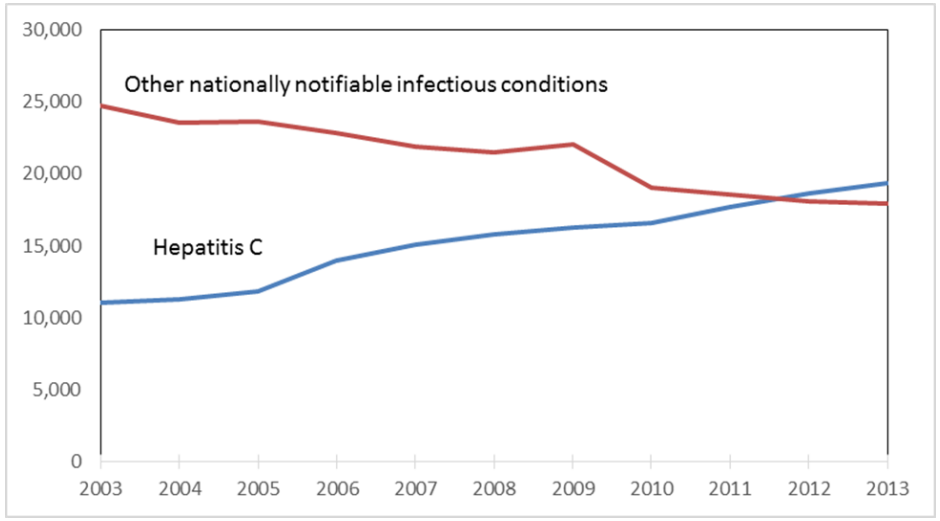
- Epidemiology and risk factors
- HCV screening algorithm
- Perinatal HCV transmission risk factors
- Indications to start HCV treatment
- Benefits of HCV treatment
- Overview of HCV direct-acting antiviral (DAA) agents

Burden of Hepatitis C in United States



Deaths from HCV and all other nationally notifiable infectious conditions from death certificates United States, 2003-2013

"The "Silent Epidemic"



This graph actually minimizes the problem

- In a study of 1600 persons who died from HCV:
  - Mean age death = 59 yrs
  - Only 19% had their HCV infection recorded on the death cert.
  - Yet 75% had clear pre-mortem evidence of liver disease (bx, dx, FIB4, etc)
  - Over 100 000 deaths/year in those diagnosed with HCV

HHS Viral Hepatitis Action Plan

- Increase the number of HCV-infected persons who are aware of their status through screening
- Link HCV-infected persons to care
- Increase number of HCV-infected persons receiving HCV treatment
- Increase number of HCV-infected persons cured

Risk factors for hepatitis C

- Injection drug use – accounts for ~60% of acute HCV infections
- History of incarceration – 29% of incarcerated persons have HCV
- Baby boomers
- Children born to HCV-infected mothers
- Percutaneous exposure – HCW or unregulated tattoo parlor
- Other: Long term hemodialysis, blood transfusion or organ transplant before July 1992, clotting factors received before 1987, persons infected with HIV
- Sexual transmission possible but low (0.07%) - Risk highest among HIV-infected MSM.
  - Condoms advisable but USPSTF doesn't recommend condoms for monogamous couples

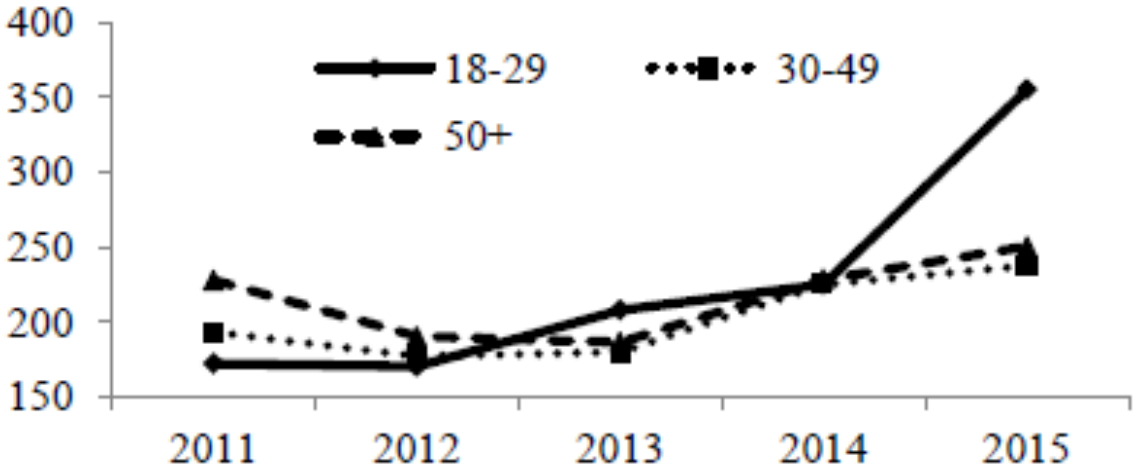
Baby Boomers (Born 1945-1965)

- Prevalence of HCV infection = 3.5%
  - 5x higher prevalence of HCV than adults born in other years
- Account for 3/4 of all chronic HCV infections among adults in the U.S.
- Account for 75% of the deaths caused by hepatitis C each year
- Majority do not know they are infected
- USPSTF recommends 1-time HCV infection screening for all baby boomers

CDC MMWR, August 17, 2012, Vol. 61, No. 4

Vertical Transmission from Mother to Child Likely to Increase

Figure. Rates of Reported HCV Cases, by Age Group (in Years) and Year — Alaska, 2011–2015

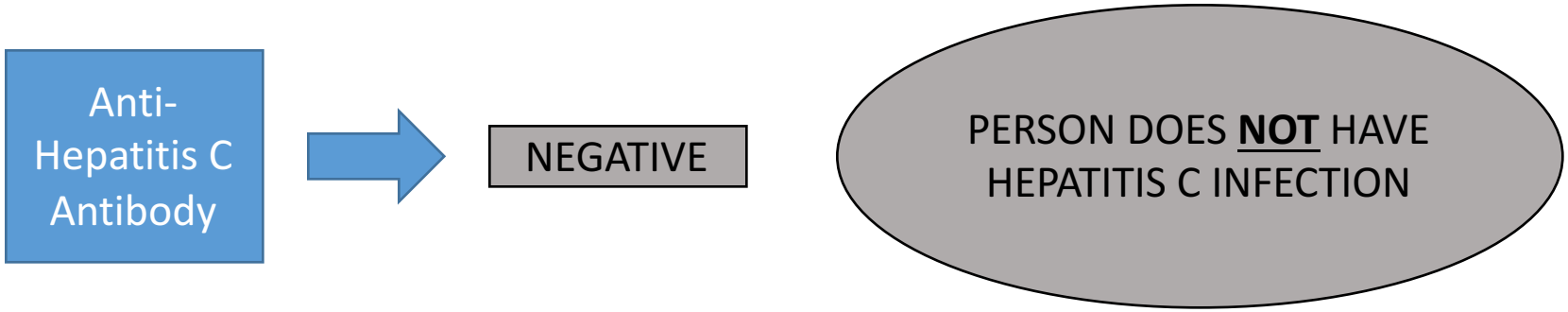


- Total of 5,888 HCV cases in Alaska 2011-15
- HCV rates for all age groups during 2011-14 ranged from 170-250/100,000 persons
- In 2015, rate among persons aged 18-29 years increased to 355/100,000
- Overall, 55% of HCV cases occurred in males; among persons aged 18-29 years, 53% were female

Hepatitis C Virus & Pregnancy

- Vertical transmission rate ~6%
- Factors associated with vertical transmission
  - HCV viremia – transmission rate directly related to degree of viremia
  - Rate up 2x higher in mothers with HIV coinfection
- Factors possibly associated with vertical transmission but link not clearly established
  - Prolonged rupture of membranes
  - Obstetric procedures such as amniocentesis and fetal scalp monitoring
- Factors not associated with vertical transmission
  - Mode of deliver - C-section delivery does not reduce risk
  - NO RISK in transmission for breastfeeding unless nipples are cracked or have open cuts and wounds.

Hepatitis C Virus Screening and Clinical Tests



- If recent exposure, test may be falsely negative
  - Repeat in 4-6 months
  - Consider HCV RNA testing.

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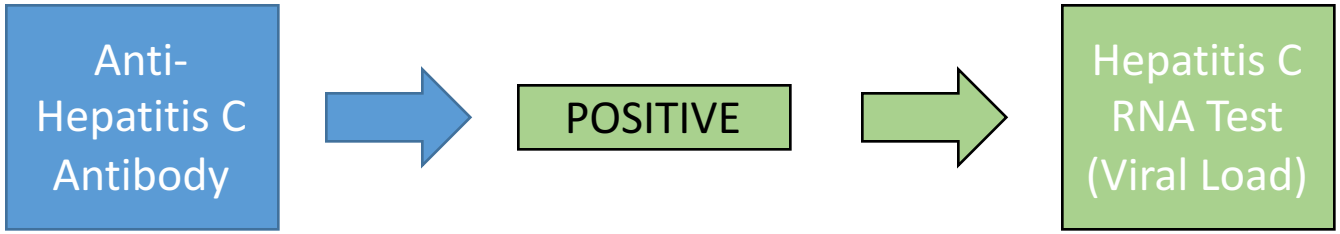
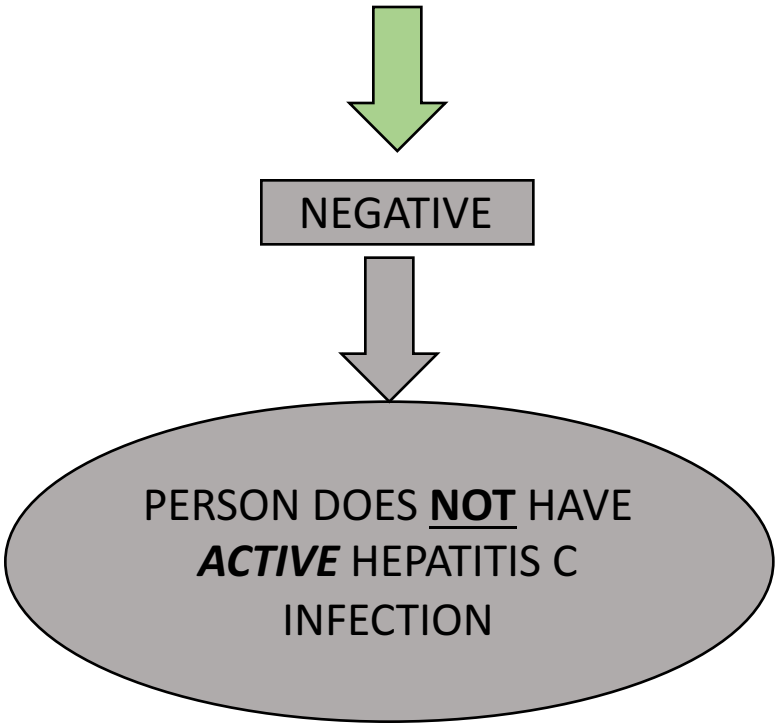
Hepatitis C Virus Screening and Clinical Tests



- This result indicates a person has been exposed to hepatitis C, but does not have an active infection.
- ~15-25% of persons clear the virus without treatment within 6-12 months postinfection.



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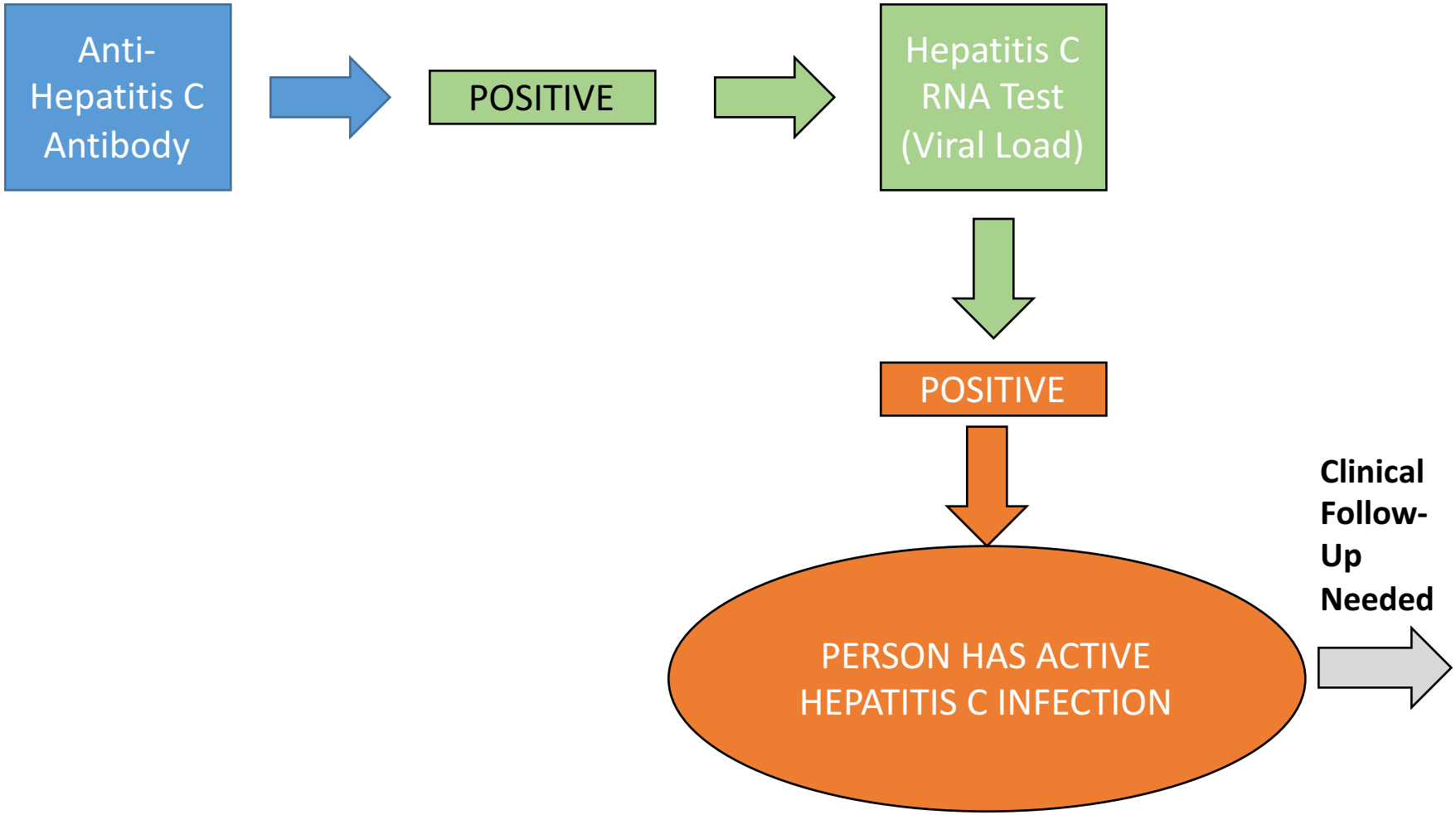
Hepatitis C Virus Screening and Clinical Tests



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HCV Screening for Infants of Mothers with HCV Infection

- HCV RNA testing as early as 3 months of age
  - 2 negative tests > 3months apart excludes infection.

- Anti-HCV Antibody test is done at 18 months or later.

Initial Clinical Management

- Assess for other liver diseases: HBV, NAFLD, Alcohol use
- Assess for degree of liver fibrosis (scarring): Determines urgency of treatment
- Counsel on precautions to reduce transmission to others such as avoid sharing razor blades, needles, toothbrushes and nail clippers
- Vaccinate against HAV, HBV and, if cirrhosis present, pneumococcal disease
- Abstain from alcohol use - >50 grams/day alcohol accelerates liver fibrosis but lesser amounts still harmful

Indications for HCV Treatment

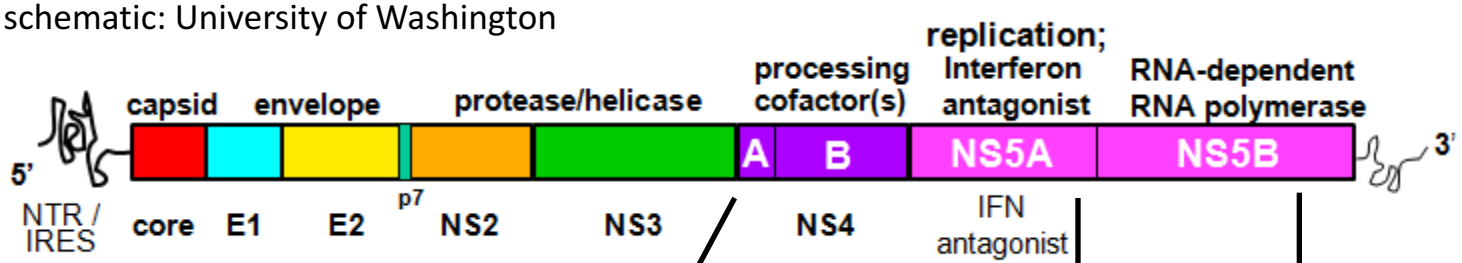
- AASLD/IDSA practice guidelines recommend treatment for all HCV patients except those with a short life expectancy
- Insurance providers might impose additional requirements for treatment
  - Alaska Medicaid authorizes treatment for persons with moderate liver fibrosis

Benefits of HCV Treatment

- Reduction in morbidity and mortality:
  - 50% resolve cirrhosis (along with signs of decompensation)
  - 70% reduction in liver cancer risk
  - 90% reduction in liver-related mortality and transplant
  - Improved quality of life (fatigue limiting activity is most commonly reported symptom)
- Reduced transmission among
  - Persons who inject drugs
  - Pregnant women - MTCT doesn’t occur if mom not viremic

Where Direct Acting Anti-Virals (DAAs) Target the Hepatitis C Virus

Virus schematic: University of Washington



NS3/4 Protease Inhibitors

~~**Boceprevir**~~

~~**Telaprevir**~~

Simeprevir

Paritaprevir

Grazoprevir

NS5A Inhibitors

Ledipasvir

Ombitasvir

Daclatasvir

Elbasvir

Velpatasvir

NS5B Inhibitors

Sofosbuvir

Dasabuvir

Considerations for Selecting a Treatment Regimen

- Drug factors: potency and barrier to resistance
- Virus factors: Genotype, resistance
- Patient factors: prior HCV treatment, cirrhosis, renal failure
- Provider factors: Formulary, expertise/familiarity

Hepatitis C Treatment Medications

Treatment length 8-24 weeks. Cure rate > 95% for most

Medications	Genotype	Common Side Effects
Daclatasvir &Sofosbuvir	1 & 3	Headache, fatigue
Elbasvir/Grazoprevir	1 & 4	Fatigue, headache, nausea
Ledipasvir/sofosbuvir	1, 4, 5, &6	Fatigue, headache
Simeprevir &Sofosbuvir	1	Fatigue, headache, nausea
Ombitasvir, Paritaprevir, ritonavir	4	Asthenia, fatigue, nausea, insomnia
Sofosbuvir/Velpatasvir	All	Headache, fatigue, nausea
Ombitasvir, Paritaprevir, ritonavir; Dasabuvir	1	Nausea, itch, insomnia

Some treatments will require ribavirin

Current Treatment Options for Pregnant Women and Children

- Pregnant women
  - Pegylated-interferon and ribavirin contraindicated
  - No approved treatments
- Children
  - Pegylated-interferon and ribavirin are approved
  - Response rates similar to adults
  - Toxic side-effect profile

Current Clinical Trials

- Ledipasvir/Sofosbuvir for 12 weeks in pregnant women[1]
- Ledipasvir/Sofosbuvir ± ribavirin for 12 or 24 weeks in children aged 12—18 years[2]
- Sofosbuvir + ribavirin for genotypes 2 and 3 in children aged 3—17 years[3]

[1] https://clinicaltrials.gov/ct2/show/NCT02683005
[2]https://clinicaltrials.gov/ct2/show/NCT02249182?term=treatment+of+hepatitis+c+in+children&rank=10
[3]https://clinicaltrials.gov/ct2/show/NCT02175758?term=treatment+of+hepatitis+c+in+children&rank=13

Most Current Recommendations

AASLD and IDSA Recommendations for Testing, Managing, and Treating Hepatitis C

Available at:

http://www.hcvguidelines.org

ANTHC Liver Diseases and Hepatitis Program Guidelines for Providers

Available at:

www.anthctoday.org/community/hep/providers

Questions?

Participants Available for Evaluation Up To 20 Years Post-Vaccination

Median years followed after 3rd HAV vaccine dose	**Median age (years) at follow-up evaluation**	**Number of participants available for follow-up by vaccine schedule**			
		A (0/1/2)	**B (0/1/6)**	**C (0/1/12)**	**All**
0.1	**5.2**	49	42	45	136
3.1	**8.1**	51	42	43	136
10.2	**15.3**	21	21	20	62
12.4	**17.6**	16	17	16	49
14.2	**19.1**	21	22	13	56
17.3	**22.4**	23	17	18	58
19.7	**24.8**	17	18	17	52

Proportion of Participants with anti-HAV ≥20 mIU/mL During Follow-Up

Median years followed after 3rd HAV vaccine dose	**Median age (years) at follow-up evaluation**	**% of participants with GMC ≥20 mIU/mL by vaccine group**		
		A (0/1/2)	**B (0/1/2)**	**C (0/1/2)**
0.1	**5.2**	98	100	100
3.1	**8.1**	96	100	100
10.2	**15.3**	100	100	100
12.4	**17.6**	81	100	100
14.2	**19.1**	86	100	100
17.3	**22.4**	87	100	94
19.7	**24.8**	77	94	94

Proportion of Participants with anti-HAV >20 mIU/mL During Follow-Up

Age (months) at vaccination (1st/2nd dose)	**Mother Anti-HAV status**	**% participants with anti-HAV ≥20 mIU/mL at time points post-vaccination**				
		1 mo	**3 years**	**7 years**	**10 years**	**15-16 years**
A) 6/12	negative	100	100	97	94	75
	positive	100	100	100	91	61
B) 12/18	negative	100	100	100	100	100
	positive	100	100	100	100	67
C) 15/24	negative	100	100	100	100	100
	positive	100	100	100	100	67