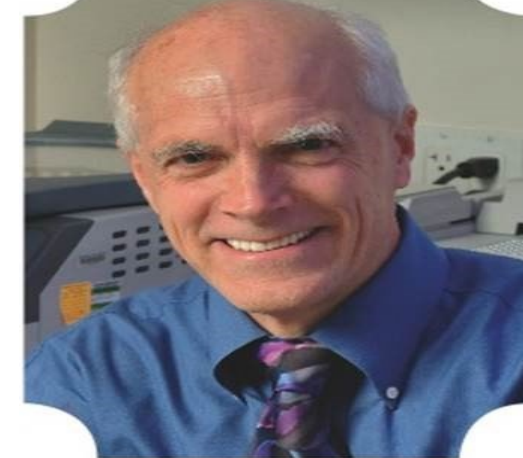




Name:



Country: Alaska USA

Affiliation: Liver Disease and Hepatitis Program

Function: Hepatologist and Researcher

Main expertise (1-2 lines): Research and public health projects in hepatitis A for 40 years

Thirty years of hepatitis A epidemiology and vaccine studies: A narrative review of lessons learned in Alaska - ScienceDirect

Brian J McMahon MD, FAASLD

Senior Consultant:

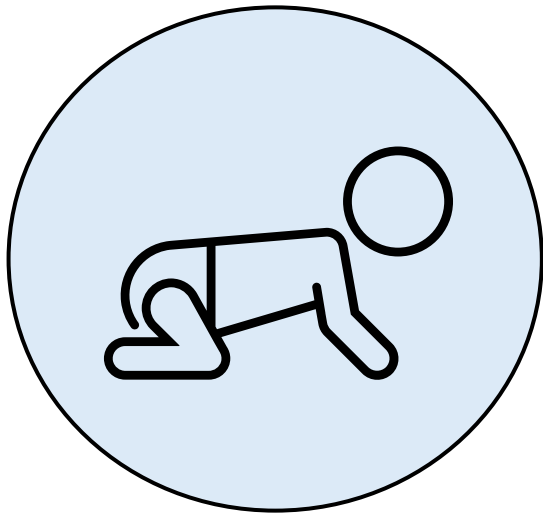
Liver Disease and Hepatitis Program

Alaska Native Tribal Health Consortium

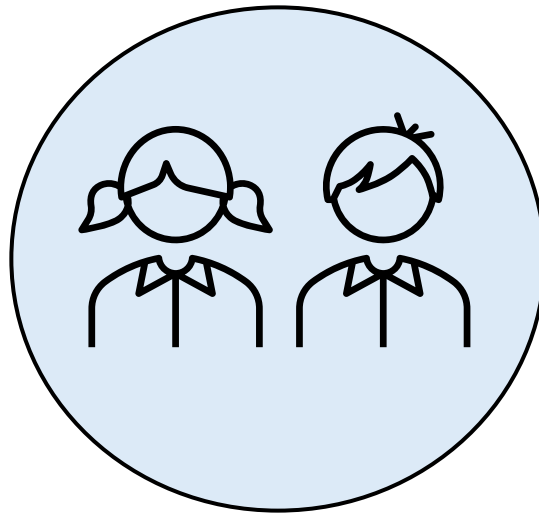
Objectives

- To review the epidemiology of hepatitis A in US, in the State of Alaska, the Alaska Native (AN) Population and the Disparity that previously but no longer existed in the past
- To highlight programs established by LDHP, Alaska Tribal Health Organizations and the State of Alaska Dept. of Health to eliminate transmission of Hepatitis A and reverse the previous disparity.
- To discuss the recent surge in acute hepatitis A in the Lower 48 states
- To present data on the long-term protection of hepatitis A vaccine from Alaska

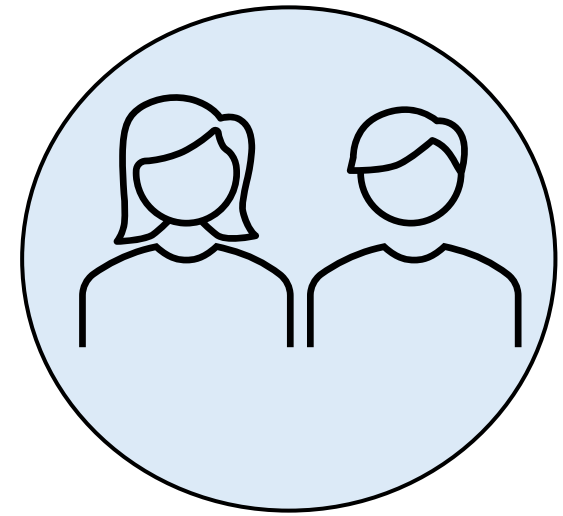
Hepatitis A vaccine recommendations in USA



**All children 12-23
months of age**



**Unvaccinated children
2-18 years of age**



**Unvaccinated adults at
high risk for HAV
infection**

Effects of Hepatitis A Outbreaks in Alaska on Communities

- Hepatitis A outbreaks in Alaska in the past occurred about every 10 years lasting 3 to 5 years
- In each rural communities the outbreak averaged 6 to 12 months
- In each community outbreak effected young persons ages 15 and under or 30 and under depending on when last epidemic in community occurred
- Children missed school and often schools had to close
- Subsistence activities were curtailed leading to food shortages
- Work was missed leading to economic hardship

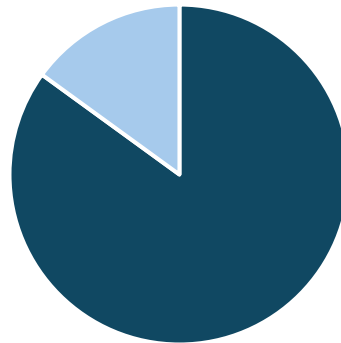
Historically, HAV was endemic in Alaska



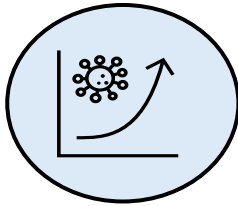
**Pre-vaccine HAV
seroprevalence in Alaska
Native people was 49%.**



**Seropositivity increased with
increasing age.**



**85% of Alaska Native people born
before 1945 were HAV seropositive.**

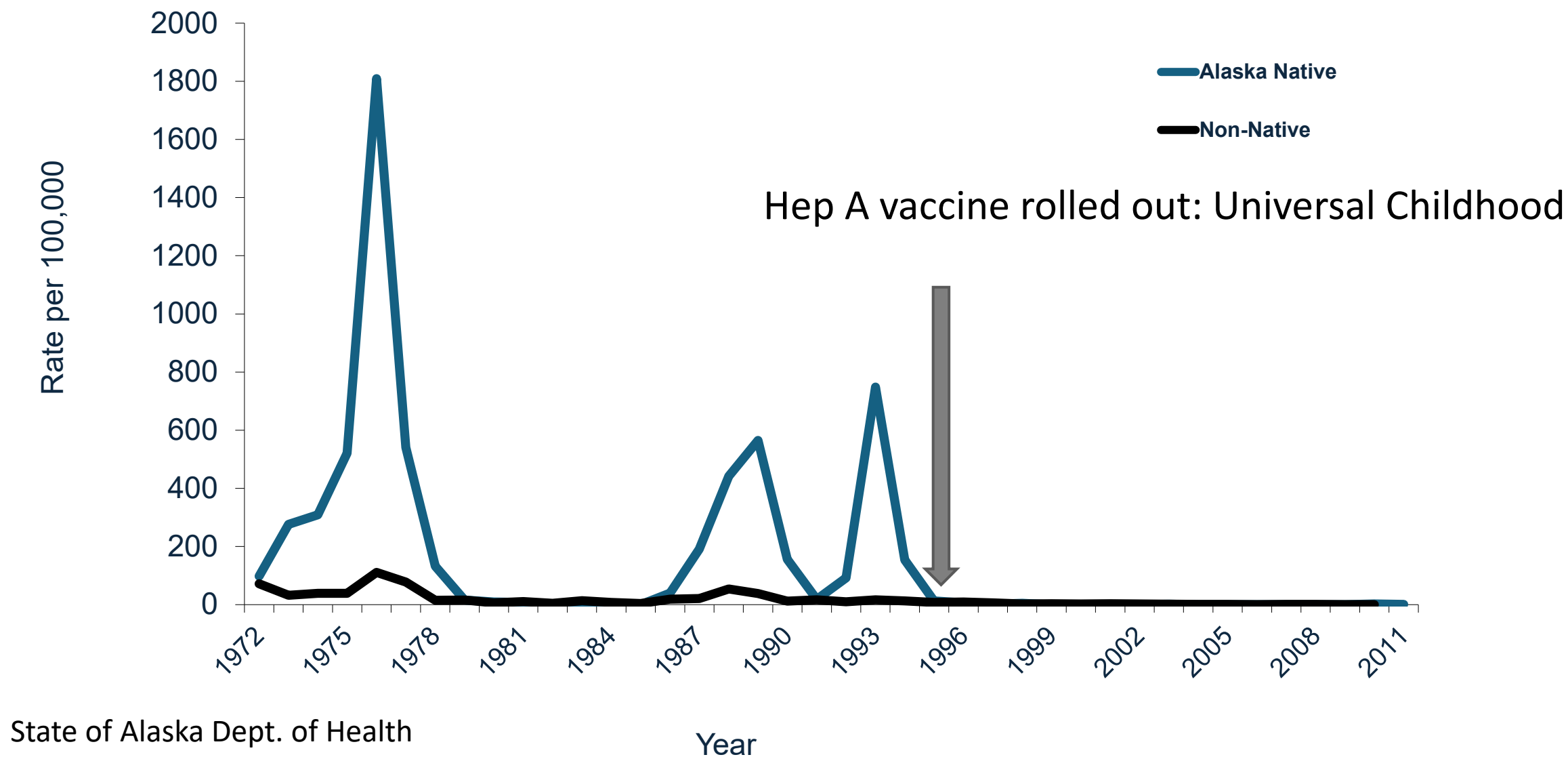


1990–1998: HAV infection rates among Alaska Native/American Indian people were **6.5 times the national average.**



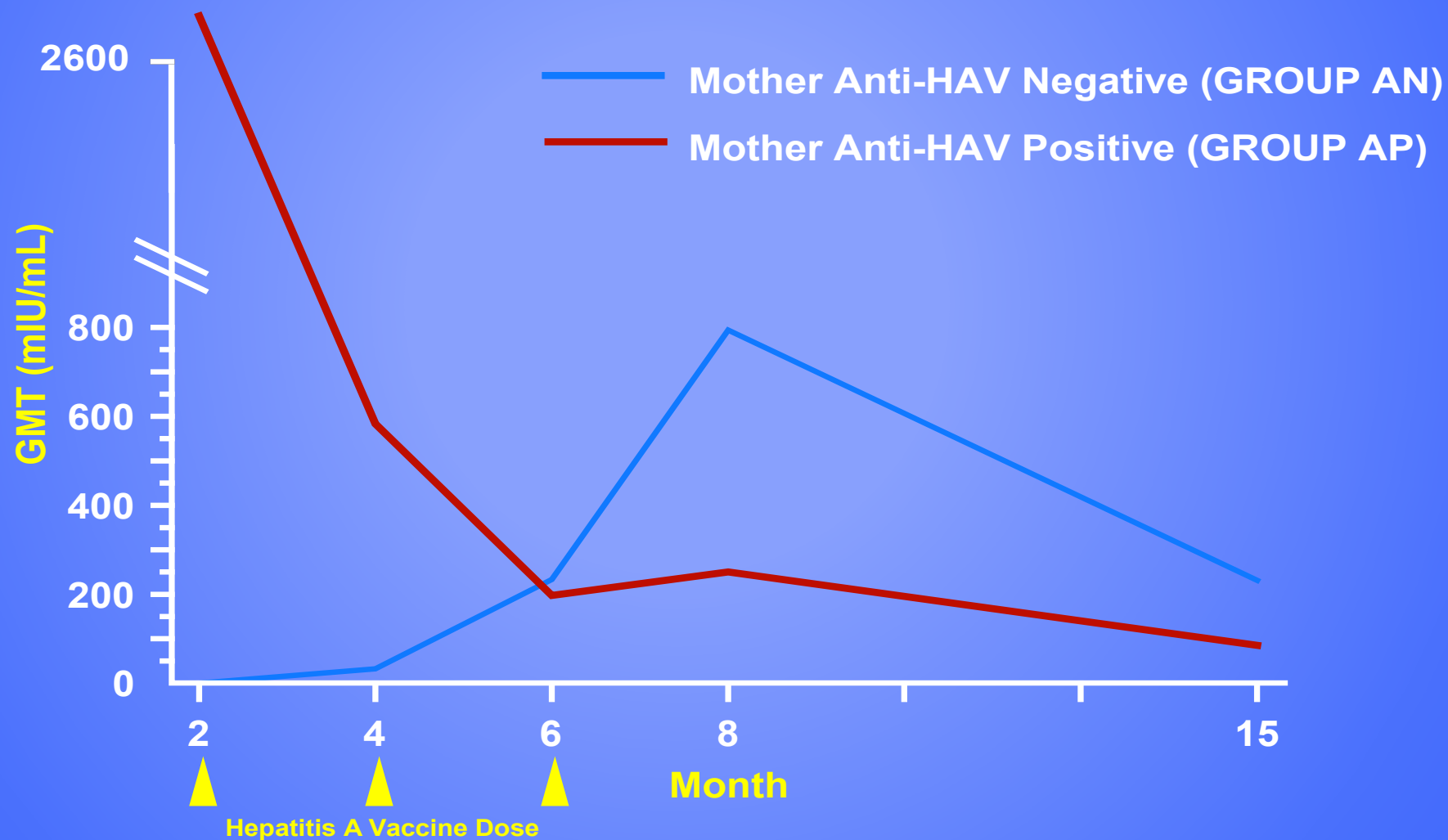
Lack of in-home piped water

In the past, large outbreaks of Hepatitis A occurred in Alaska



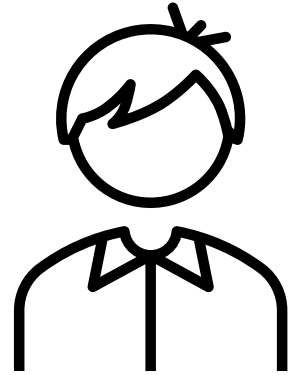
Hepatitis A Vaccine Studies in Alaska

ANTI-HAV TITERS IN INFANTS RECEIVING HEPATITIS A VACCINE AT 2, 4 and 6 MONTHS OF AGE



Pre-licensure studies in Alaska (1)

3–6 years old



360 EL.U

Months:

0



1



2



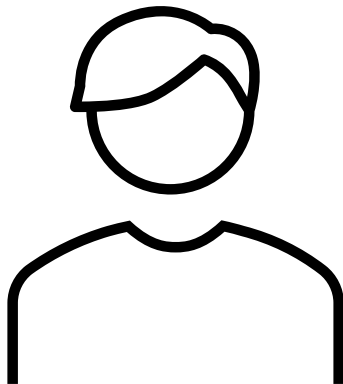
6



12



Adult



740 EL.U

Months:

0



1



6



100% of children & adults achieved protection after the third dose.

90-96% of people achieved protection after first dose

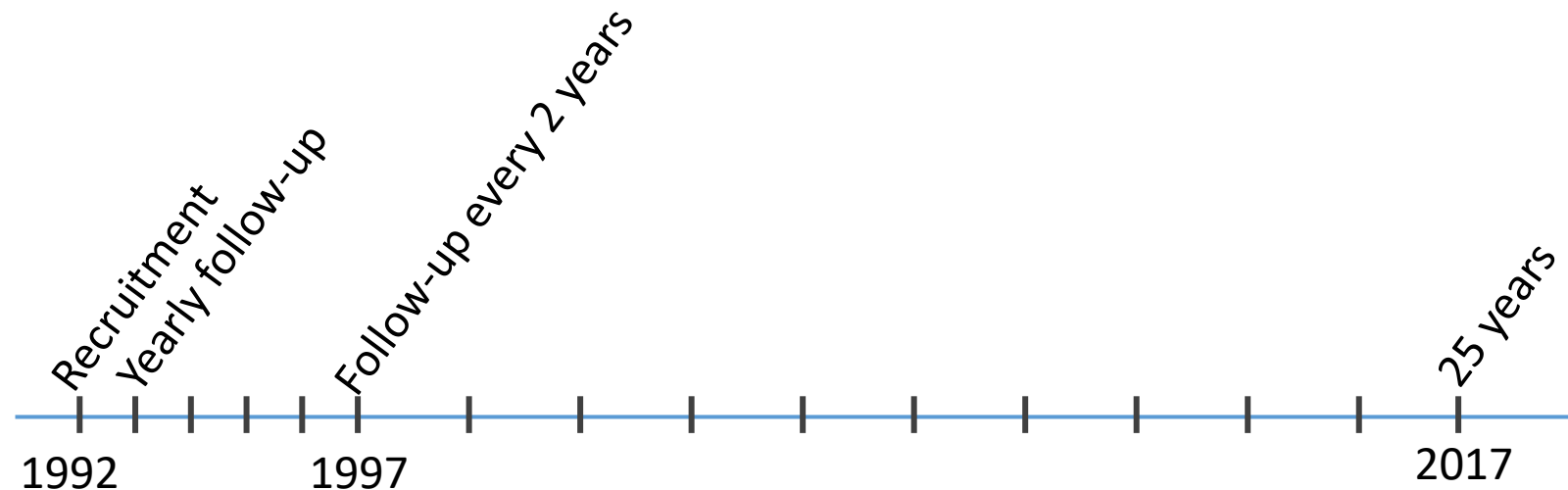
Hepatitis A vaccine cohort in Alaskan Children

Who:

- 143 children from Anchorage: Phase 3 trial for FDA licensure approval
 - Age 3-6 years: Randomized 3 groups, each received 3 doses of 720 EU vaccine
 - Vaccinated with currently licensed recombinant HAV vaccine
 - Total HAV antigen administered was only 75% of the current 2-dose schedule

When:

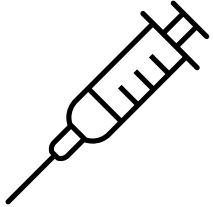
- Recruited in 1992-1993: 97% of Group 1 and 100 present Group 2 responded
- Yearly follow-up until 1997, then follow-up every 2-3 years for 30 years total



Pre-licensure studies in Alaska (2)

1440 EL.U



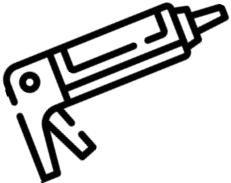

Intramuscular
injection

15 days



80% of participants
protected



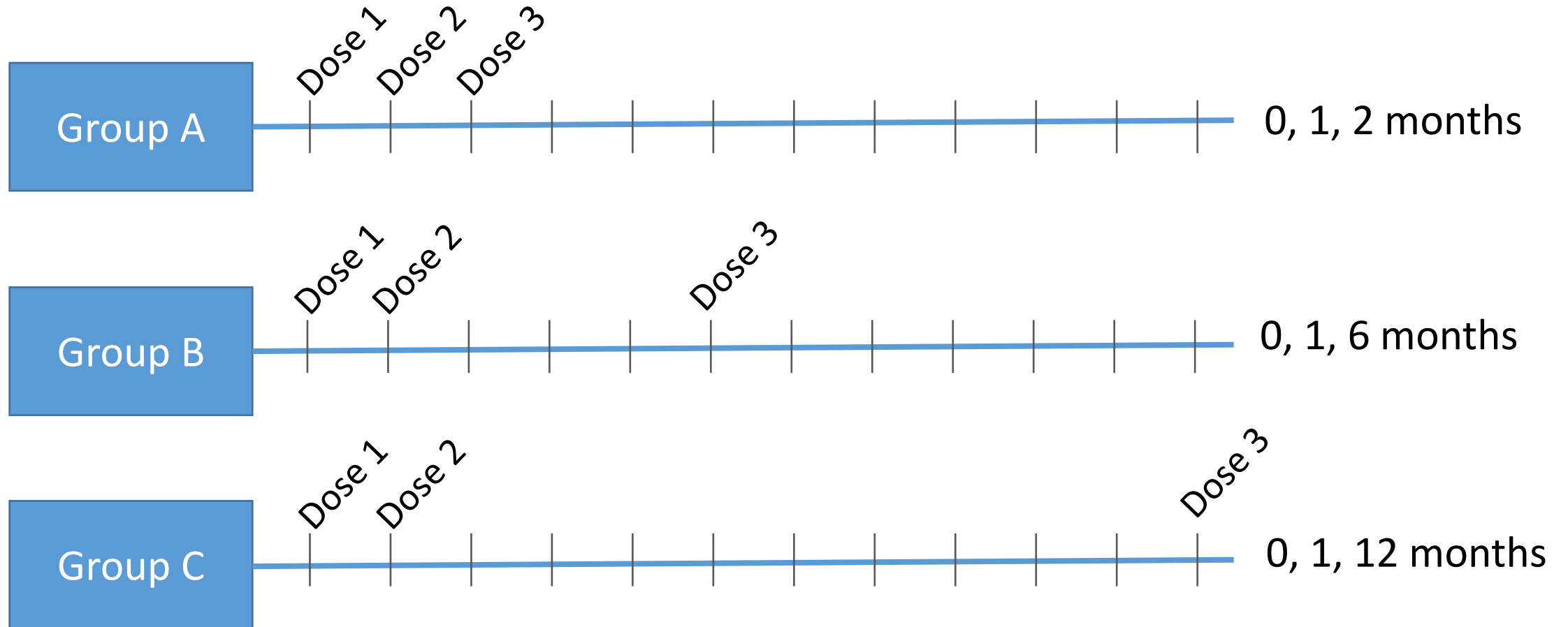

Jet injector



71% of participants
protected

One dose of HepA
vaccine shortly after
a known exposure
offers protection
regardless of
administration
method.

Three hepatitis A vaccine dosing schedules



Alaska Study in Infants and Toddlers

- Convenience sample of 3 groups: Vaccine started at 6 months of age, 12 months of age and 15 months of age after all routine childhood vaccines had been administered
 - Results HAV antibody one month post 1st dose:

Date of 1 st Vx Dose	Mothers HAV antibody	% Infants Anti-HAV positive	GMC mIU/ml	GMC Range
6 Months	Negative	54	49	33.6-71.5
	Positive	94	173	109-272
12 Months	Negative	60	44	37.5-77.9
	Positive	64	48	31.6-63.2
15 months	Negative	68	65	46.1-90.6
	Positive	73	70	42.1-115.2

Bell BP, Negus S, Fiore AE, Plotnik J, Dhotre KB, Williams J, Shapiro DN, McMahon BJ. Immunogenicity of an inactivated hepatitis A vaccine in infants and young children *Pediatric Infectious Diseases* 2007;26:116-122

Anti-HAV GMT in Adults after One Dose of Hepatitis A Vaccine 1440 EU

- Alaska Hepatitis A Study in Hospital Employees: Anti-HAV GMT
 - After one dose:
 - Day 15: 71 to 80% had anti-HAV >20 mIU/ml detectable. GMC 28-56-42.86 mIU/ml.
 - Day 30: 84 to 92% had anti-HAV >20 mIU/ml. GMC 58.96-142.03.
 - 1 month post 2nd dose. 100% anti-HAV+: GMC 1344.53 to 1633.7 mIU/ml
- Alaska Hepatitis A Outbreak study
 - 30 days dose #1
 - Age 1-2 years: GMC 416 mIU/ml.
 - Ages 3-40 years: GMC 202-254 mIU/ml
 - 20-31 months post 2nd dose:
 - 0-2 years: GMC 760 mIU/ml
 - 3-64 years: GMC 1538-2144 mIU/ml

McMahon BJ, Beller M, Williams J, Schloss M, Tanti H, Bulkow L. A program to control an outbreak of hepatitis A in Alaska by using an inactivated hepatitis vaccine. Archives of Pediatrics and Adolescent Medicine 1996;150:733-739.

Table 5. Anti-HAV Response After 1 Dose of Hepatitis A Vaccine by Age*

Age, y	n	Anti-HAV >20 mIU, No. (%)	95% CI	GMT	95% CI
1-2	32	32 (100)	89-100	416	288-602
3-9	11	10 (91)	59-100	202	99-413
10-19	44	38 (86)	73-95	189	125-287
20-40	31	29 (94)	79-99	254	174-373

* HAV indicates hepatitis A virus; CI, confidence interval; and GMT, geometric mean titer.

Williams JL, Bruden JA, Cagle HH, McMahon BJ, et al. Hepatitis A vaccine: immunogenicity following administration of a delayed immunization schedule in infants, children and adults. *Vaccine*. 2003;21:3208-11.

Alaska Hepatitis A Study to Stop an epidemic of Hepatitis A

- A large epidemic of hepatitis A occurred in Alaska from 1986 to 1995.
- Acute cases went from rural community to community lasting 3-9 months in each community until herd immunity occurred
- Children missed weeks of school and families were unable to gather subsistence foods
- Gamma globulin only slowed down transmission for a month or two

McMahon BJ, Meller M and Williams et al. Arch. Pediatrics Adolesc Med (JAMA Peds) 1996;150:733-739

Peach D, McMahon BJ, Bulkow L et al. J Infect Dis 2002;186:1081-5

Hurlburt KJ, McMahon BJ, Deubner H, Hsu-Trawinski B, Williams JL, Kowdley KV. Prevalence of hepatitis A virus infection on population immunity levels: Bristol Bay, Alaska. J Infectious Dis 2002; 186:1081-85

Stopping an Epidemic of HAV in Alaska

- We received 5,000 doses of HAV vaccine from the manufacturer prior to licensure but after we had conducted our HAV vaccine trial
- Four Tribal Health Organizations volunteered for the trial and volunteered staff and one, an airplane.
- Study was IRB and Tribal cleared and participants signed informed consent
- 4,930 susceptible persons in 25 rural communities received one dose of vaccine
- Within 4-8 weeks of vaccination the outbreak stopped in 24 communities where 80% of susceptible age group persons were vaccinated while decreasing but continuing on for 1-year in one community where 50% were vaccinated

McMahon BJ, Beller M, Williams J, Schloss M, Tanti H, Bulkow L. A program to control an outbreak of hepatitis A in Alaska by using an inactivated hepatitis vaccine. Archives of Pediatrics and Adolescent Medicine 1996;150:733-739.

Administration of a Delayed Booster Dose

- After licensure, we returned to all communities 20 to 31 months later to administer dose #2 to participants
- 268 persons negative prior to dose #1 were tested before and after the booster dose
- 16% had anti-HAV GMT <20 mIU/ml, below purported protection level at the time of the booster dose
- All responded to the booster with GMT between 1538 and 2144 mIU/ml for all those over age 2-years but 1/2 for those under

Williams JL, Bruden JA, Cagle HH, McMahon BJ, Negus SE, Christensen CJ, Snowball MM, Bulkow LR, Fox-Leyva, LK. Hepatitis A vaccine: immunogenicity following administration of a delayed immunization schedule in infants, children and adults. *Vaccine*. 2003;21:3208-11.

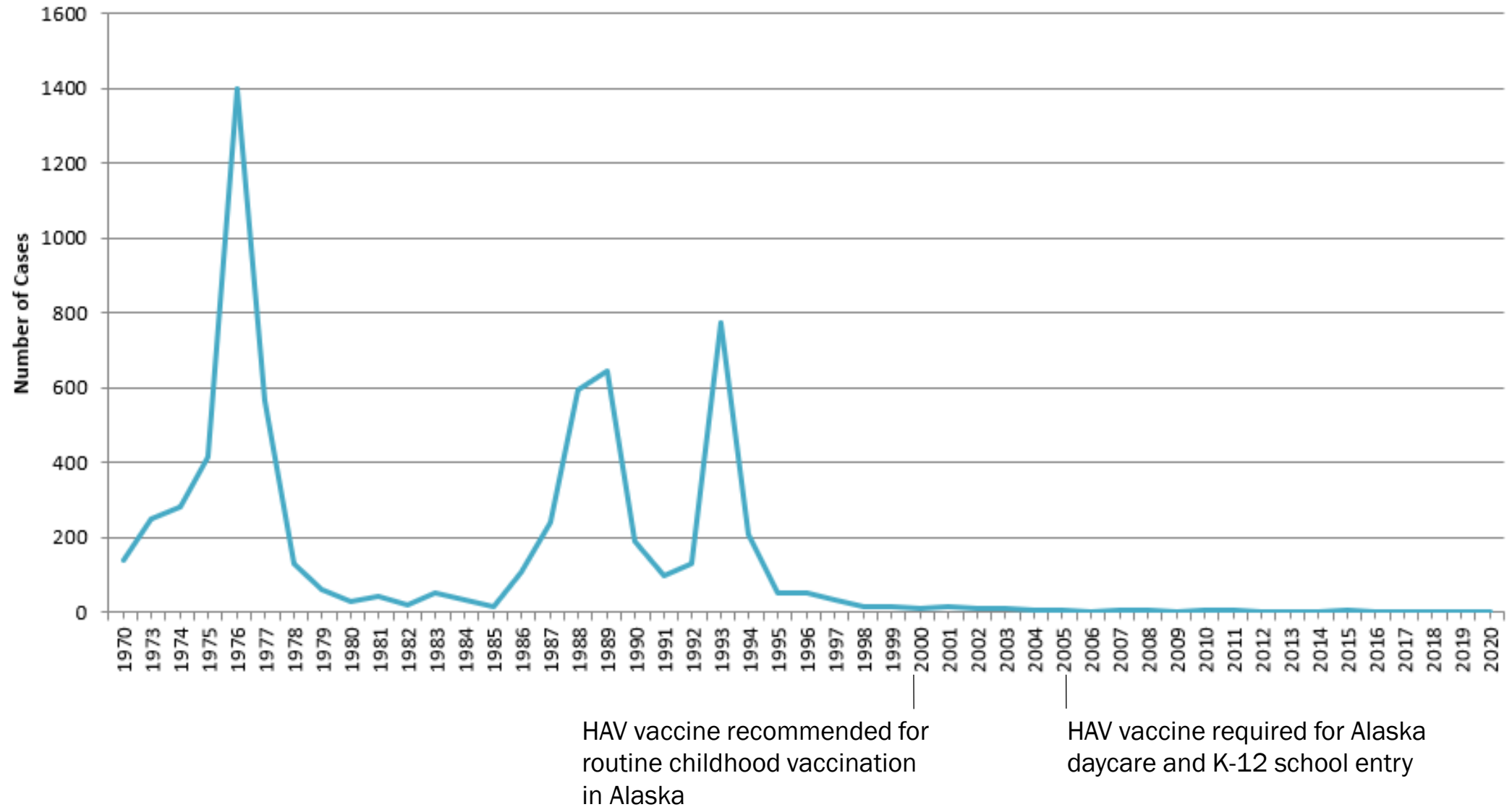
Alaska: The First US State to Offer Universal Hepatitis A Vaccine

- Beginning in 1996, Hepatitis A vaccine offered to all children ages 2-18
 - 2006: All children > 1 year old
- Immunization results to date:
 - Hepatitis A vaccine is required for school entry
 - > 95% children vaccinated by 5-years old
 - 31% of all adults ≥ 18 years have received at least one dose
 - Only 8 cases of acute hepatitis A were reported in Alaska in 2017-2022
 - All were travel related or linked to a person who had traveled
 - **Lowest rate in the entire world: Yea for Alaska!!**

Balta VA, McMahon BJ, Moore K, Stevenson T, Scobie HM, Thirty years of hepatitis A epidemiology and vaccine studies: A narrative review of lessons learned in Alaska. *Annals of Epidemiology* (2026)110108.

www.sciencedirect.com/journal/annals-of-epidemiology120

Reported Cases of Hepatitis A - Alaska, 1970-2020



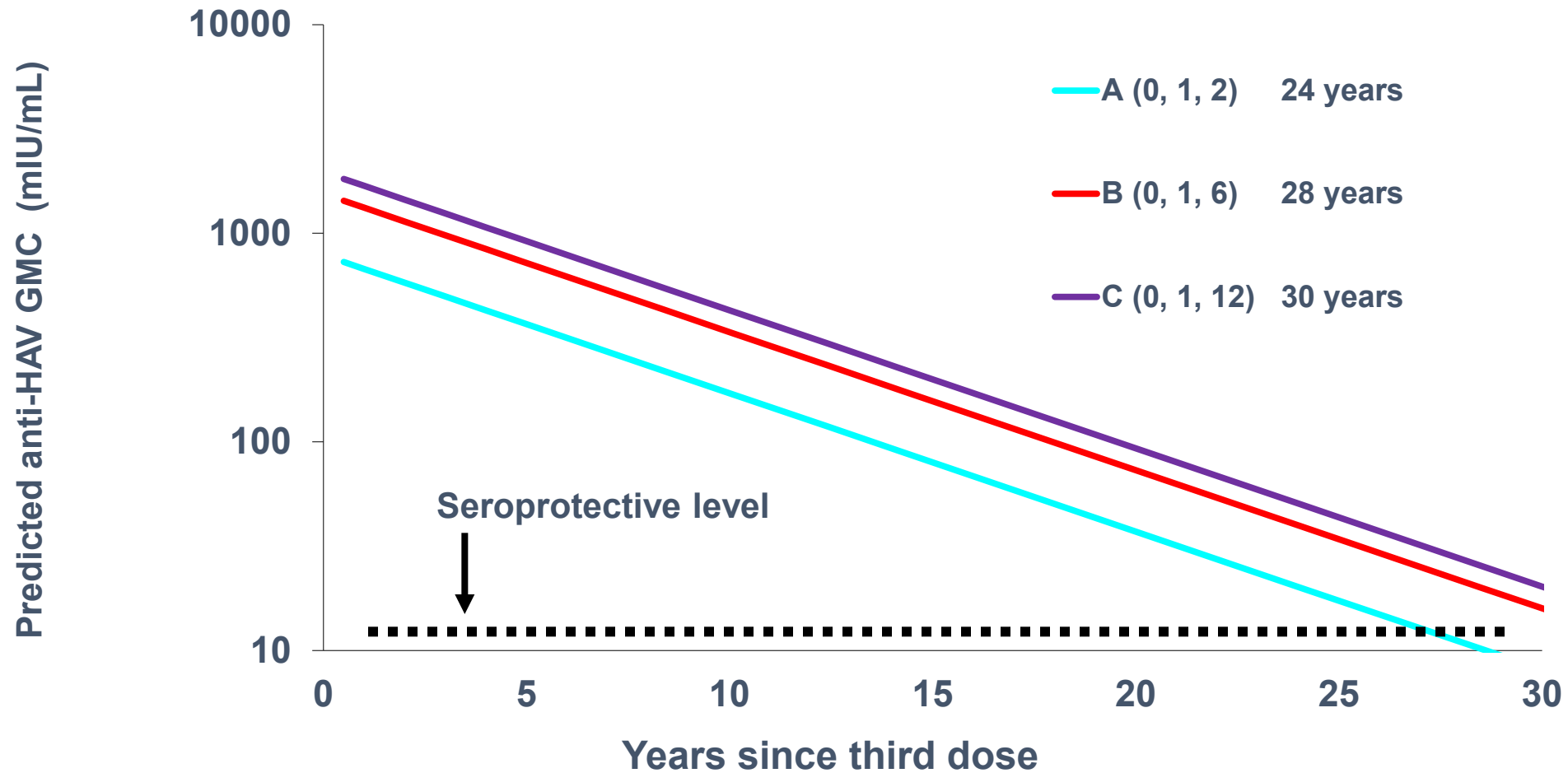
25 Year Follow-up of Participants Who Received HAV Vaccine as Children

- 25 years after the initial series
 - 81.4% still had anti-HAV present (mean 91 GMT anti-HAV level 91.5 mIU/ml)
 - Children randomized to the 0, 1, 2 month dose had significantly lower proportion with anti-HAV at 25 years > 20 mIU/ml (60%)
 - Children randomized to the 0, 1, 6 or 0, 1, 12 month schedule had significantly higher proportion with anti-HAV > 20 mIU/ml (90%) and significantly higher GMT anti-HAV. (p=0.004)
 - This 3 dose series is no longer utilized (now 2 dose schedule 0 and 6 months with 25% more antigen) but this study shows long-term persistence of anti-HAV

Rasmaswamy M, Bruden D, Nolen, Mosites, Snowball M, Nelson NP Bruce B, McMahon BJ.

Hepatitis Vaccine Immunogenicity 25 Years after Vaccination in Alaska A long-term children 25. J of Med Virology 2020:1-4.

Predicted Antibody GMC Over Time, by Vaccination Schedule at 14 Year Follow-Up



Long-Term Follow-up Hepatitis A Infant and Toddler Vaccine Study

- Follow-up 20 years: proportion GMT anti-HAV <20 mIU/ml: time 1st dose
 - Vaccinated at 6 months: 70% of those anti-HAV+ moms, 38% negative moms
 - Vaccinated at 12 months: 50% with mothers anti-HAV+, 13% negative moms
 - Vaccinated 15 months: 30% anti-HAV+ mothers, 16% anti-HAV negative moms
 - GMC range 11 to 54 mIU/ml

Scobie H, Negus S, Stevenson T, Bressler S, Bruden D, Simmons BC, Snowgall S, Hofmeister MG, Bruce M, Townshend-Bulson L, Fischer M, McMahon B. Factors associated with hepatitis A seropositivity at 23 years after childhood vaccination. Open Forum Infectious Disease. DOI: 10.1093/ofid/ofae417

HepA Vaccine Coverage, US

- Children¹, birth year 2017-2018
 - 77.7% for children by age 35 months, ≥2 doses
 - 87.0% for children by age 24 months, ≥1 dose
- Adolescents², 2020
 - 82.1% for adolescents age 13-17 years, ≥2 doses
- Adults³, 2018
 - 11.9% for adults ≥19 years, ≥2 doses; Travelers, 18.9%; Chronic liver disease, 15.8%
 - 17.5% for adults 19-49 years, ≥2 doses; Travelers, 24.9%; Chronic liver disease, 16.9%
 - 6.2% for adults ≥50 years, ≥2 doses

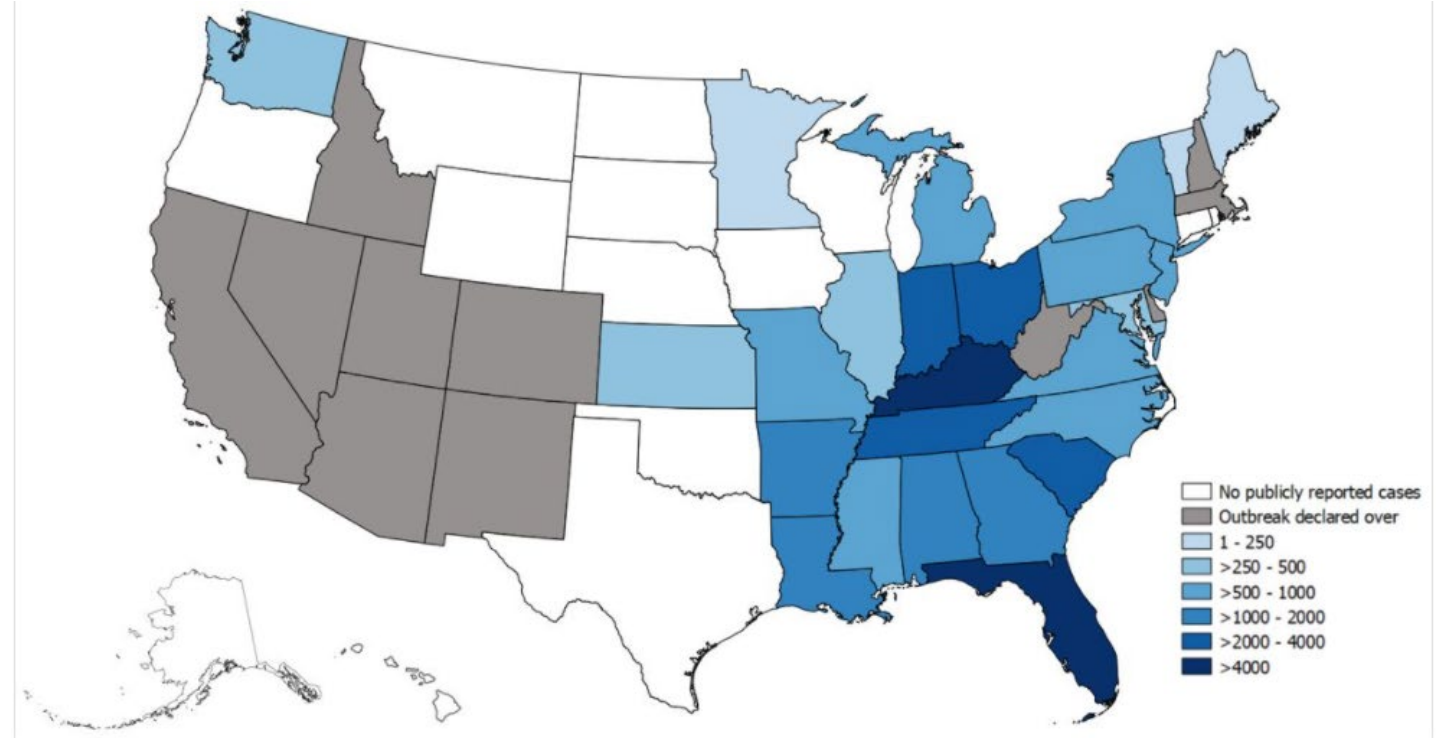
1. Hill HA, et al. MMWR 2021 Oct 15;70(41):1435-1440. [Vaccination Coverage by Age 24 Months Among Children Born in 2017 and 2018 - National Immunization Survey-Child, United States, 2018-2020 - PubMed \(nih.gov\)](#)

2. Pingali, et al. MMWR 2021; 69(42): 1506-1511. [National, Regional, State, and Selected Local Area Vaccination Coverage Among Adolescents Aged 13-17 Years - United States, 2020 - PubMed \(nih.gov\)](#)

3. Lu, et al. MMWR 2021; 70(3);1-26. [Surveillance of Vaccination Coverage Among Adult Populations — United States, 2018 \(cdc.gov\); SUPPLEMENTARY BOX 3. Estimated proportion of adults aged ≥19 years who received hepatitis A and hepatitis B vaccines, by age group, increased-risk status, and race/ethnicity — National Health Interview Survey, United States, 2018 \(cdc.gov\)](#)

Hepatitis A Virus Outbreaks, United States, 2016–2022

- State-reported outbreak information from 37 states
(July 2016 – January 14, 2022)
 - Total cases: **43,648**
 - Hospitalizations: **26,627 (61%)**
 - Deaths: **420**



<https://www.cdc.gov/hepatitis/hepAoutbreak> (accessed January 18, 2022)

Total Reported Cases of Hepatitis A in Alaska by Year 2018-2023: All Races

Year	Total Number of Acute Hepatitis A Cases	
	Incidence/100,000 (all travel related)	
• 2018	1	0.125/100,000
• 2019	2	0.25/100,000
• 2020	1	0.125/100,000
• 2021	2	0.125/100,000
• 2022	2	0.25/100,000
• 2023	0	0.00/100,000

Conclusions

- Hepatitis A infection rates have dropped dramatically among AI/AN people
 - Alaskan people of all races and ethnicities have not been affected by outbreaks in the lower 48 possibly due to
 - Earlier implementation of universal childhood vaccination
 - Higher rates of vaccination in Alaska Native Adults
- Hepatitis A vaccine protection lasts at least 25 years after initial immunization series and could last for a lifetime; 30-year data is being analyzed currently
- Universal vaccination of all adults should be considered to prevent transmission from travelers to endemic areas of the world and outbreaks