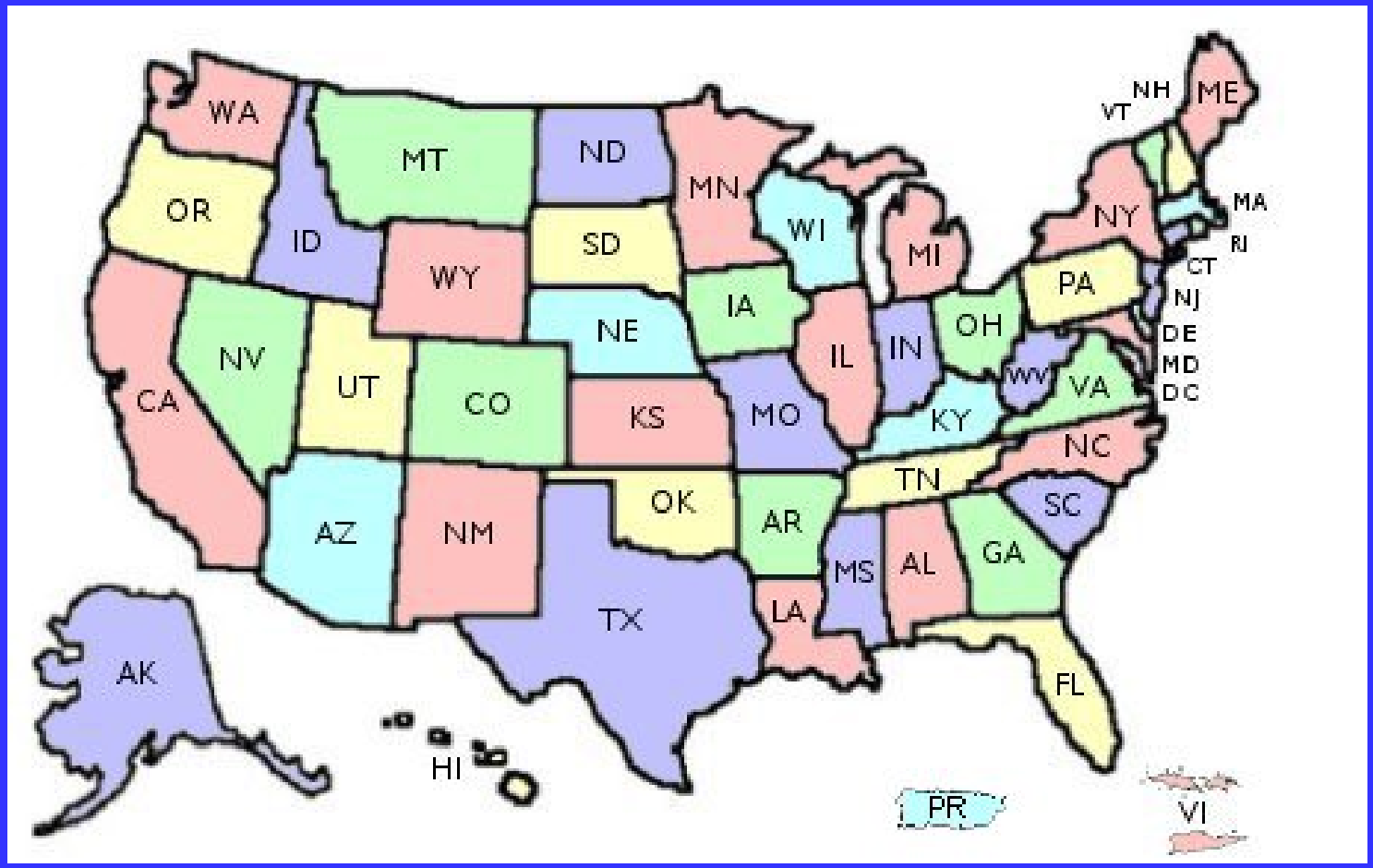
Programs for Chronic HBV and HCV in Alaska Natives

Brian J McMahon MD, Liver Disease and Hepatitis Program Alaska Native Medical Center and Arctic Investigations Program, CDC

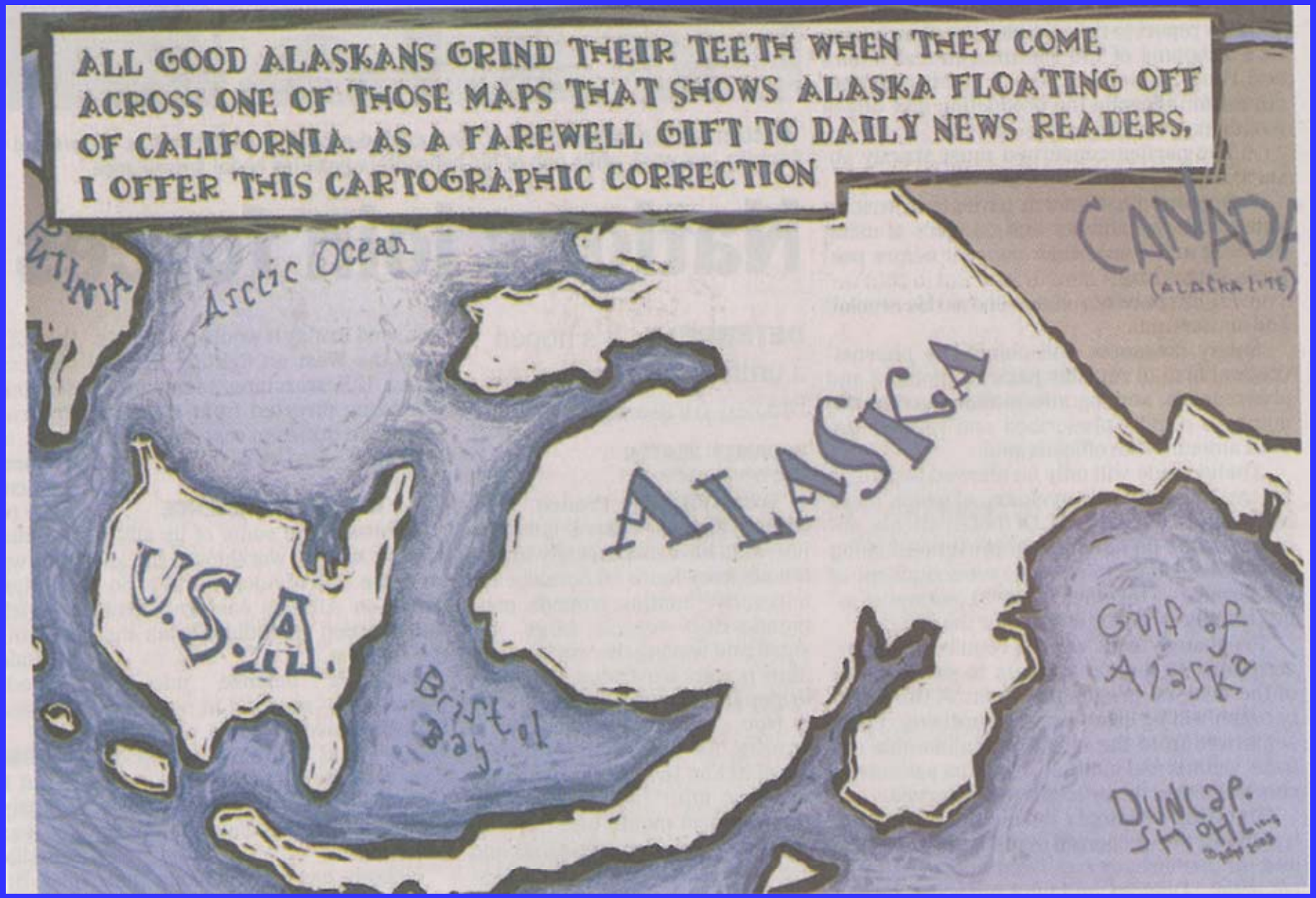
Misconceptions about Alaska

- Alaska is not part of Canada
- You can see Russia from Alaska (but not from Sarah Palin’s house
- Contrary to Fox News, the Arctic ice is thinning
- Contrary to TV weatherman's maps, Alaska is not an island off California

How Young Children in UNITED STATES draw US MAP



Politically Correct Map of Alaska in Relation to Lower 48 States

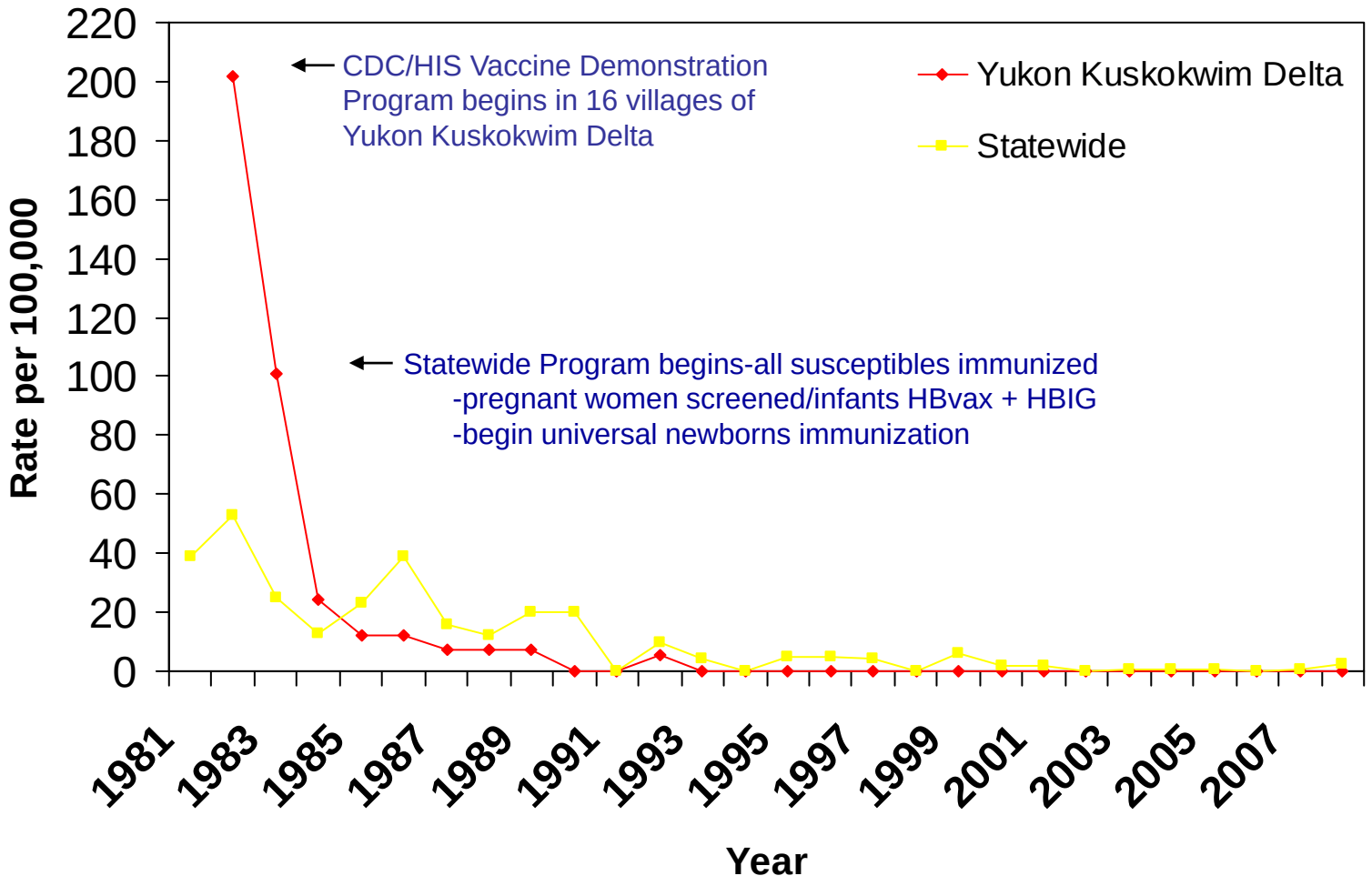


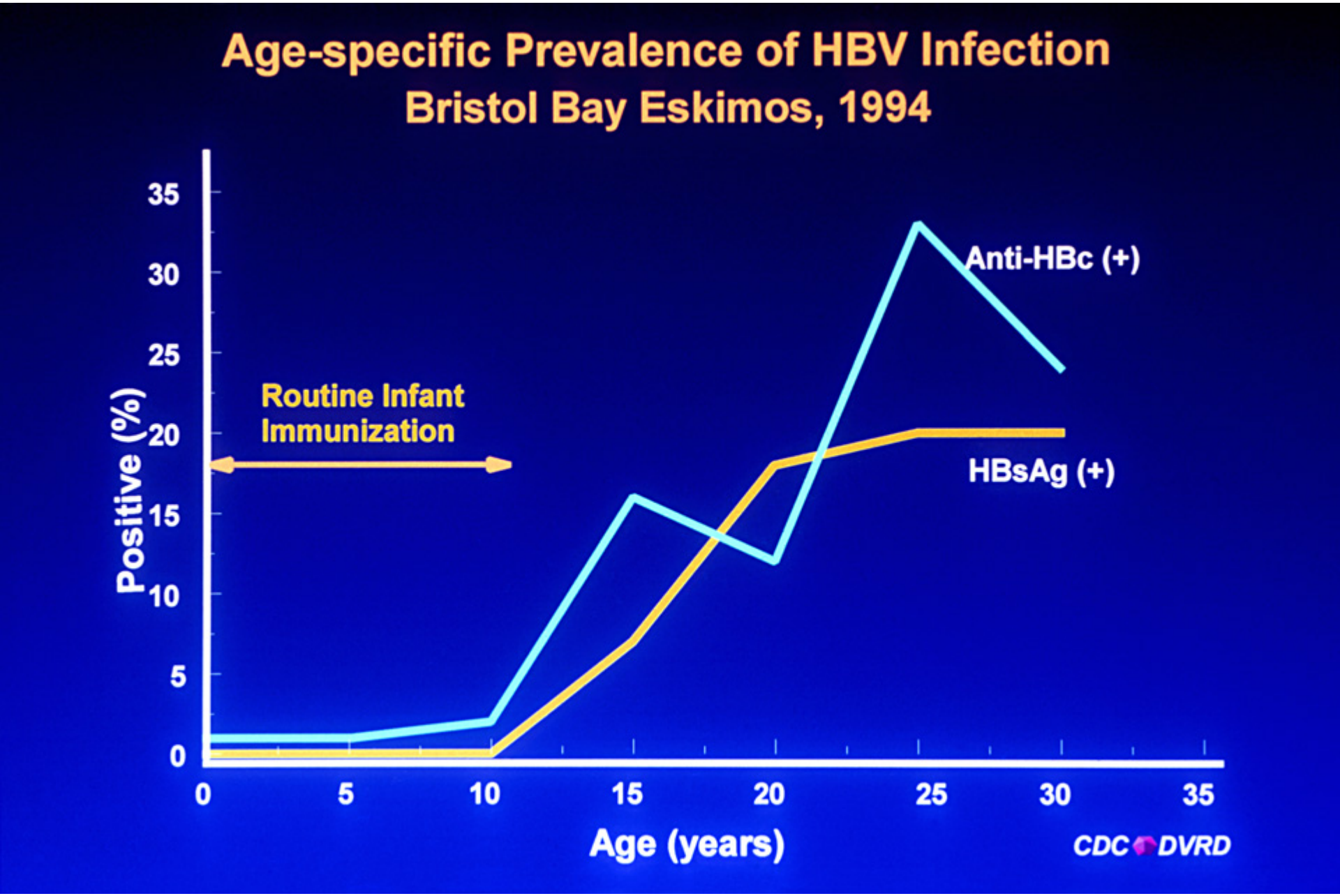
Alaska Hepatitis B Program

- 1978: Establishment of a registry of persons found to be HBsAg-positive
- AN Hepatitis B Control Program:1983-87: 53,000 Alaska Natives screened and 40,000 susceptible were vaccinated plus universal newborn vaccination

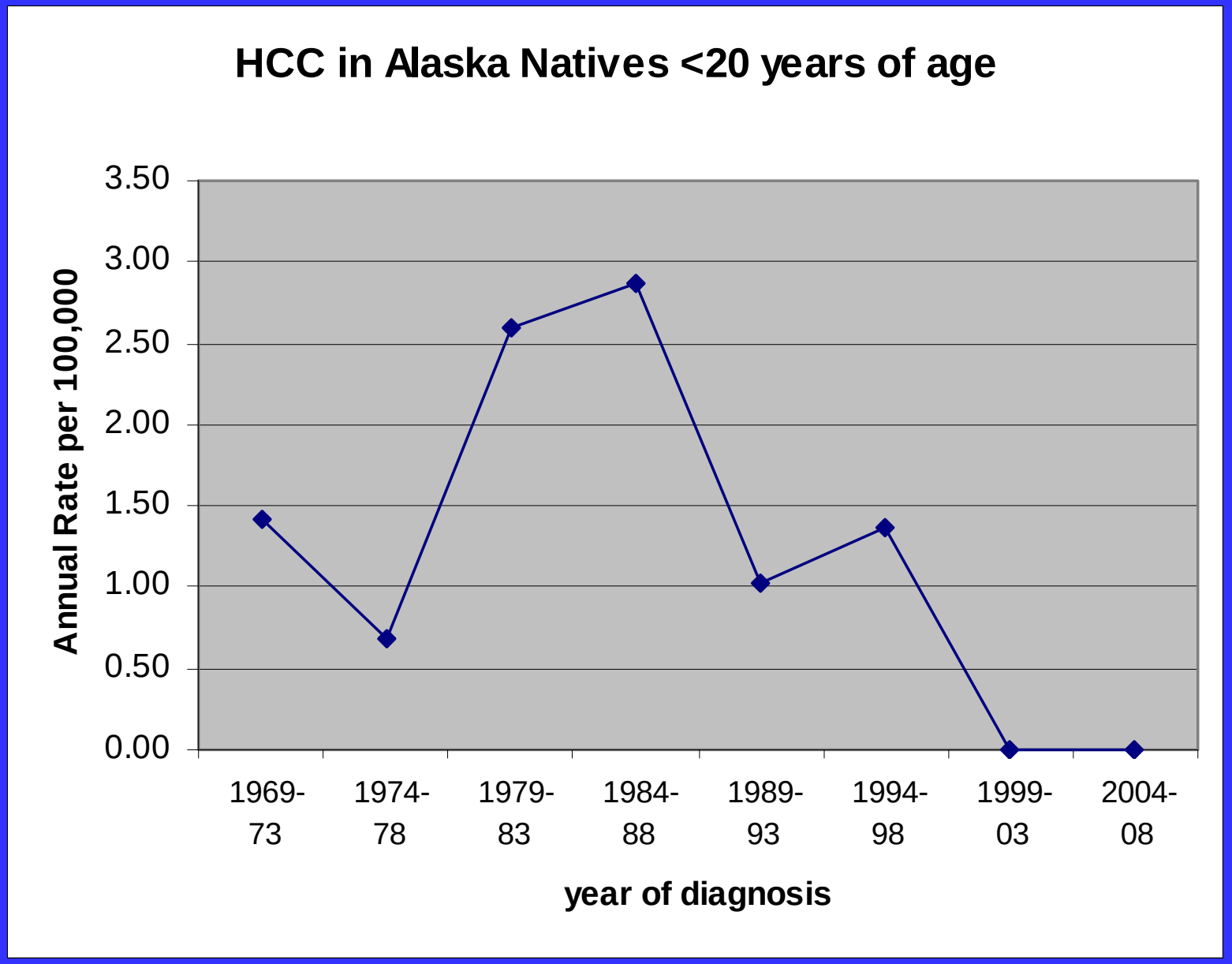
Lancet, 1987; 330:1134-1136

Incidence Symptomatic Hepatitis B in Alaska Native Peoples 1981- 2008





J Infect Dis 2000;181:413-418



P value for trend = 0.002

The Chronic HBV Alaska Cohort

- 1560 HBsAg-positive chronically infected persons were found: population-based cohort
- All clinical and lab data computerized
- Median follow-up of cohort: 21 years
- Median age at entry: 20 years
- Median age at last follow-up: 41 years
- Five HBV genotypes: 6 sub-types found
- Over 20,000 stored sera on cohort
- Computerized program to send letters to patients every 6 months

ANTHC Program to Follow Hepatitis B Carriers

- Reminder Letter every 6 months to patient;
- Lists of patients to draw blood on goes to CHAP, Regional Hospital and provider
- Blood drawn by CHAP or hospital lab, spun down and sent to ANMC lab
- ANMC tests for ALT, AST, AFP, HBeAg/anti-HBe
- Hepatitis B RN and Brian McMahon check all results on computer weekly (about 2 hours)
- If initial ALT, AST and AFP WNL computer generated letter sent to patient informing them of normal results.

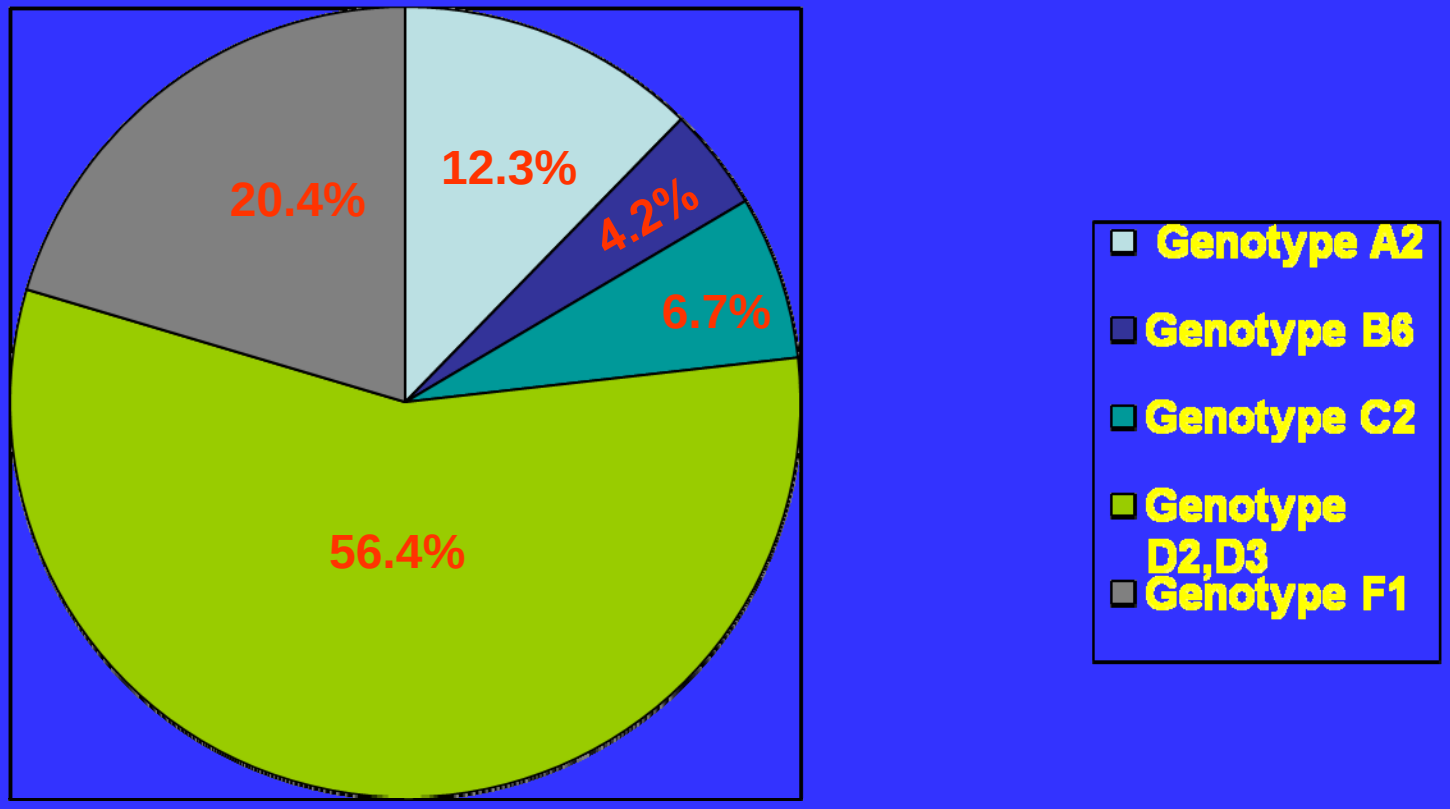
ANTHC Program to Follow Hepatitis B Carriers Continued

- If ALT or AST > UNL: Patient evaluation
  - HBV DNA level
  - History including medication use, history recent Alcohol use, history diabetes or elevated cholesterol or triglycerides
  - BMI: Need height and weight to calculate
  - Liver panel and CBC, HCV and HDV
  - Autoimmune markers in females if HBV DNA < 2,000 IU/ml

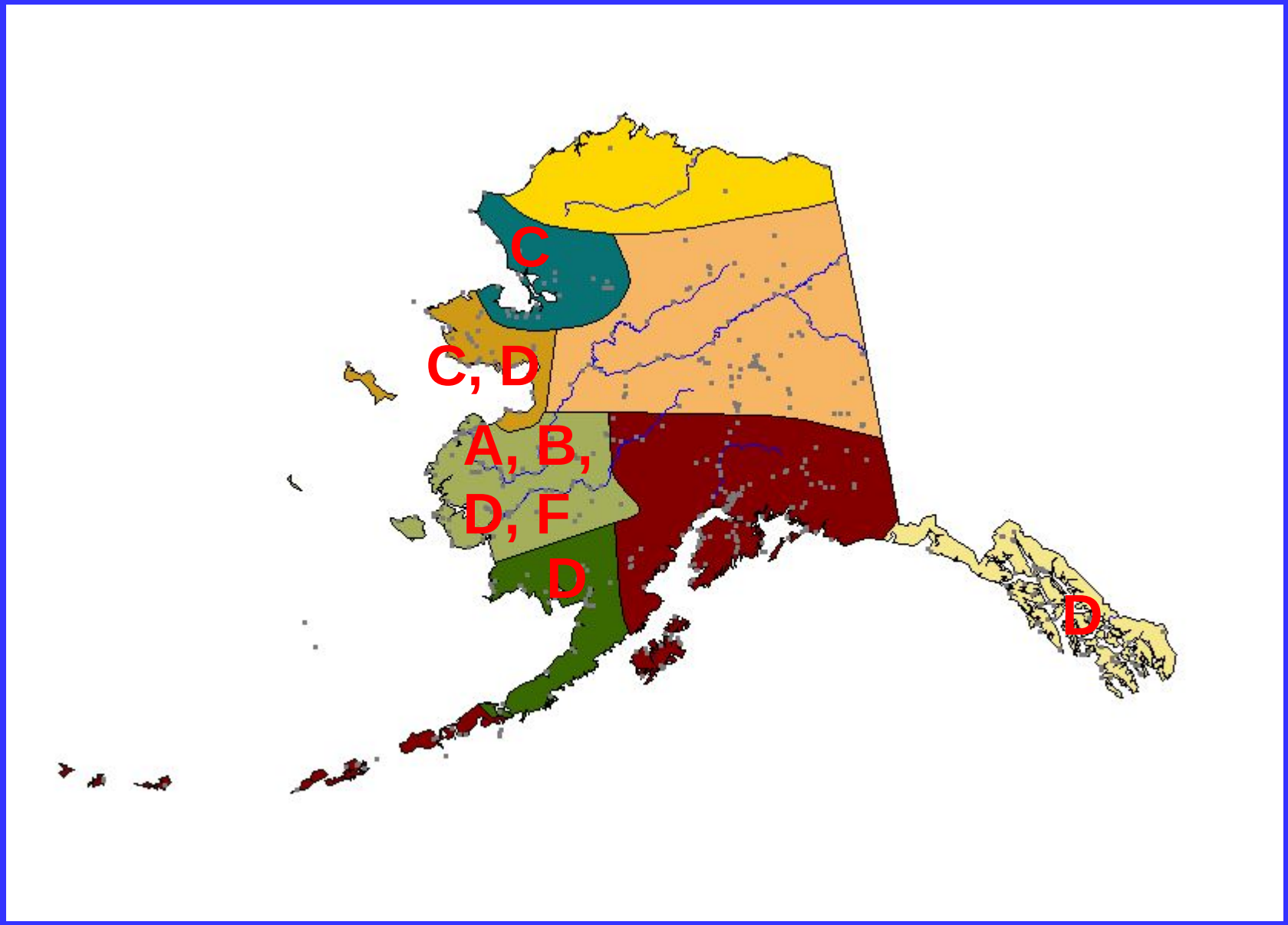
Which Patients Receive further Evaluation?

- Persons with AFP > 10ng/ml are referred for ultrasound done at nearest hospital, reviewed by teleradiography
- Patients with elevated ALT and HBV DNA > 2,000 IU/ml are recommended for a liver biopsy at ANMC to see if they need treatment
- Patients with moderate or severe inflammation or fibrosis ≥ Metavir 2 treated

HBV Genotypes in Alaska Natives



Geographic Distribution of HBV Genotypes in Alaska Natives



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

Gastroenterology 2007;133:1452-57

*P<.001 genotype C vs. other genotypes

Characteristics of HBV Genotypes

- Genotype A2 and D associated with HCC in older persons mean age > 60 years
- Genotype C associated with:
  - HCC in middle age persons ~ age 50
  - More flares of ALT >2 X ULN
- Genotype F1 associated HCC in children and young adults; mean age 22 years
- Genotype B6: Similar to B1 Japan: no HCC or liver decompensation to date

Results of Follow-up

- 50% persistently normal ALT; 49%, one or more ALT elevations: Etiology
  - Chronic hepatitis B** 24%
  - Heavy ETOH use 28%
  - NAFLD 25%
  - Other/unknown 23%

Alaska Natives and American Indians in Alaska with Hepatitis C

- Anti-HCV positive AN/AI 1,994
- Total number enrolled in study 1,201

Conclusions: Epidemiology of HCV in Alaska Natives

- Prevalence of HCV within NHANES estimates for US
- Risk Factor distribution same as US
- Proportion who recovered from HCV same as NHANES study
- Genotype distribution similar to NHANES except slightly increased proportion of genotype 3

Hepatitis C Complications

- ESLD Total: 122
  - ESLD without HCC: 105
  - ESLD with HCC: 17
  - Liver transplant: 5
- HCC Total: 29
  - HCC with ESLD 18 (3 living)
  - HCC without ESLD 11 (5 living)
- Total All Complications: 133

What is Killing HCV Infected? Patients Alaska HCV Outcome Study

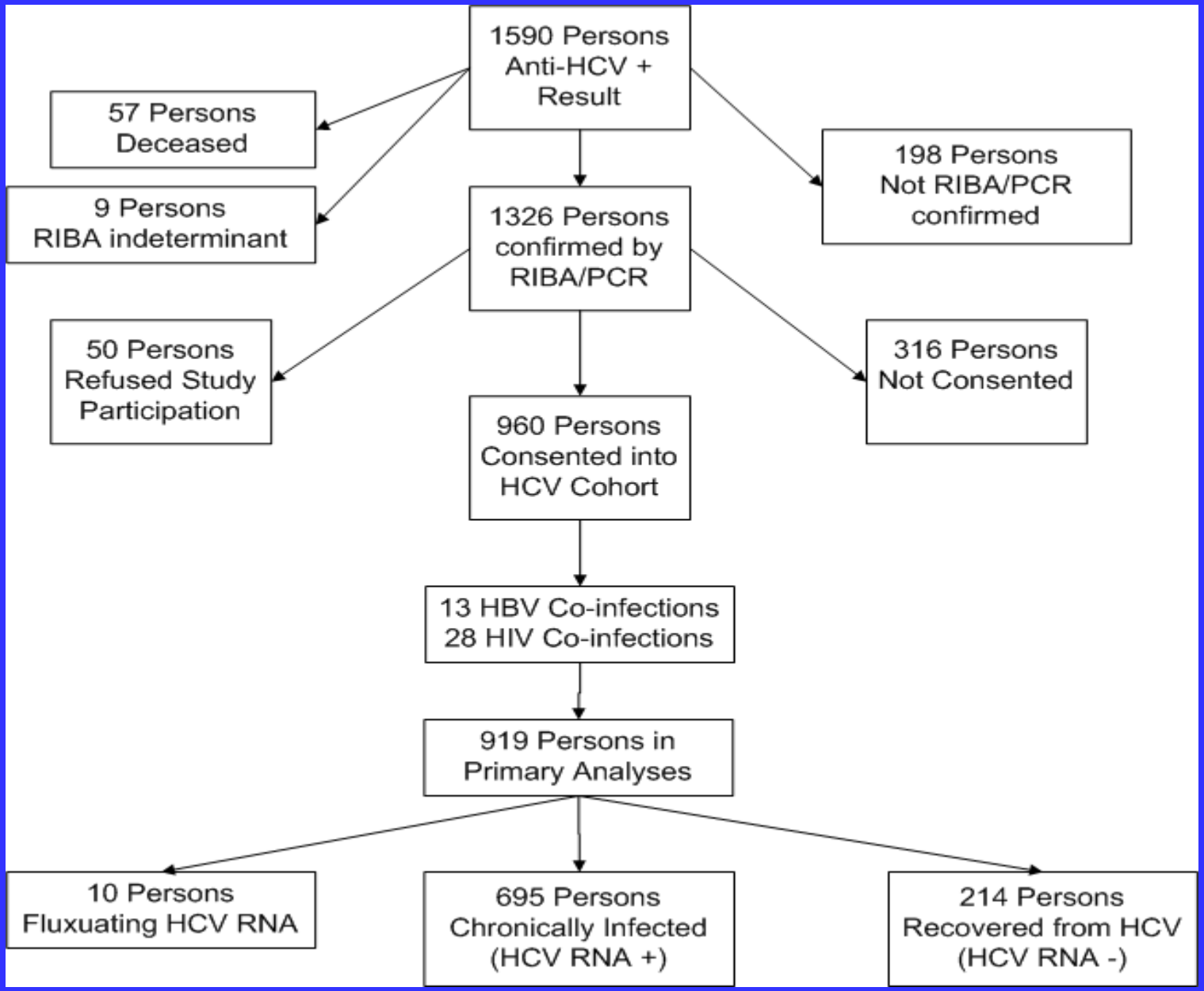
- Retrospective-prospective population-based study
- 960 patients followed 1994-2005
  - 695 chronic HCV; 214 recovered (RIBA +)
  - Mean years prospectively: 7.2 years
  - Mean years retrospectively: 12.1 years

McMahon et al Gastroenterology 2010; in press

HCV Outcome Study: Initial Evaluation

- Alcohol usage measured at enrollment
  - 13% consumed ≥ 50gms ETOH/day
- Incidence calculated per 100 person years of follow-up
  - End stage liver disease
  - Liver related death
  - HCC
- Persons with chronic HCV were compared to those who recovered.

Figure: Flow Diagram of HCV Positive Alaska Natives in Outcome Study 1992-2005



Incidence End Stage Liver Disease per 100 Person Years

Factors	Chronic HCV	Recovered HCV	P Value
Alcohol ≥50 gms/day	3.21	5.69	P=0.13
Alcohol <50 gms/day	1.58	0.36	P=0.002

Incidence Liver Related Death per 100 Person Years

Factors	Chronic HCV	Recovered HCV	P Value
Alcohol ≥50 gms/day	2.28 vs.	3.50	P=0.34
Alcohol <50 gms/day	0.77	0.09	P=0.01

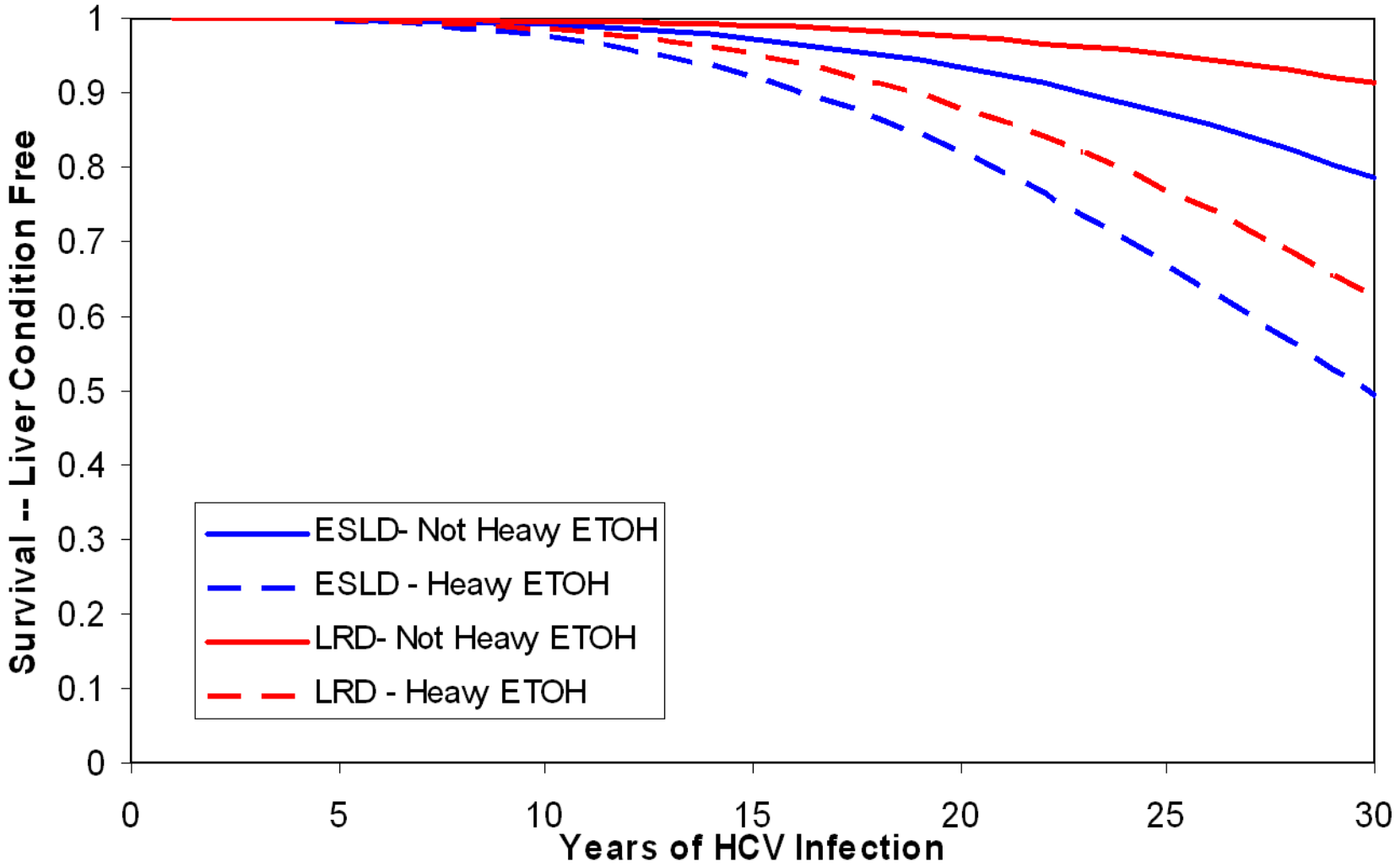
Factors Associated with Developing End Stage Liver Disease in Alaska Native Persons (AN) with Chronic HCV

- Univariate Analysis
  - Heavy alcohol use ($p = 0.004$)
  - older age at infection ($p < 0.001$)
  - AFP > 8 ng/ml ($p < 0.0001$)
  - AST/ALT ≥ 1 ($p < 0.001$)
  - HCV RNA level ($p = 0.02$)
- Multivariate analysis
  - older age
  - heavy alcohol use
  - genotype 3
- Not associated: anti-HBc, diabetes, sex, BMI

Mortality in Alaska Natives with HCV Infection vs. Those without

- AN persons with chronic HCV are 17 times more likely to die a liver related death than rest of the US population as a whole
- AN persons who recovered from HCV are 12 times more likely to die a liver related death than AN population

Survival Probability for free from end stage liver disease (ESLD) or liver-related death (LRD)



Predicted probabilities are calculated for a person infected with HCV at 25 years of age

Difficulties in Treating HCV in Developed Countries

- Many patients are difficult to reach
- Many have medical or psychiatric contraindications
- Bottom line: > 50% of HCV infected patients will be difficult to treat even with universal health care and addition of newer medications

HEPATITIS C TREATMENT ELIGIBILITY STUDY

- Aim of Study
- To examine treatment barriers for Alaska Natives with chronic hepatitis C virus (HCV) infection

2003 Results:
Reasons not treated (n = 90)

Reason	Number (%)
Did not keep appointments	32 (35.6%)
Alcohol or drug abuse within 6 months	16 (17%)
Patient decision to defer treatment	16 (17%)
Liver biopsy without fibrosis or normal ALT	8 (8.5%)
Psychiatric condition	7 (7.4%)
Concurrent medical condition	6 (6.4%)
Decompensated cirrhosis	3 (3.3%)
Age > 65 years	2 (2.2%)

Intervention Between 2003 and 2009

- Developed computerized program to send letters to all persons who were:
  - HCV RNA positive
    - In our consented cohort
    - Not in our consented cohort
    - Anti-HCV-positive but not ever tested for HCV RNA

2007 Results: Reasons not treated (n = 132)

Reason	Number (%)
Patient decision to defer treatment	36 (27.3%)
Alcohol or drug abuse within 6 months	29 (22%)
Did not keep appointments	24 (18.2%)
Concurrent medical condition	12 (9.1%)
Psychiatric condition	9 (6.8%)
Decompensated cirrhosis	7 (5.3%)
Considering treatment/treatment planned	7 (5.3%)
Liver biopsy without fibrosis or normal ALT	4 (3.0%)
Age > 65	2 (1.5%)
Other	2 (1.5%)

Studies on Patients with HCV Eligible for Treatment

	Cleveland	VA St. Louis	ANMC 2003	ANMC 2007
Patients	293	557	94	146
Not adhere	37%	56%	35.6%	18.2%
Contra-indication	34%	27%	17.3%	21.2%
Drug use	13%	17%	17%	22%
Defer Rx	11%	27%	17%	27.3%
LFT WNL	5%	5%	8.5%	3.0%
No. (%) Rx	83 (28%)	77 (14%)	4 (4.3%)	14 (9.6%)

TREATMENT OUTCOMES

Genotype	Treated	Discontinued *	Failed	Relapsed	Responded
1	34	20 (59%)	7	1	6 (18%)
2	21	5 (24%)	2	1	13 (62%)
3	15	5 (33%)	3	0	7 (47%)
Total	70	30 (43%)	12	2	26 (37%)

* P = 0.01 for discontinuation rate of genotype 1 versus 2&3 combined

TREATMENT IN THE REAL WORLD

- Few patients actually complete treatment
- Veterans Administration Study (2009)

  Total patients with HCV Infection: 134,000

  Completed treatment: 2,394/10,641 (22.5%)

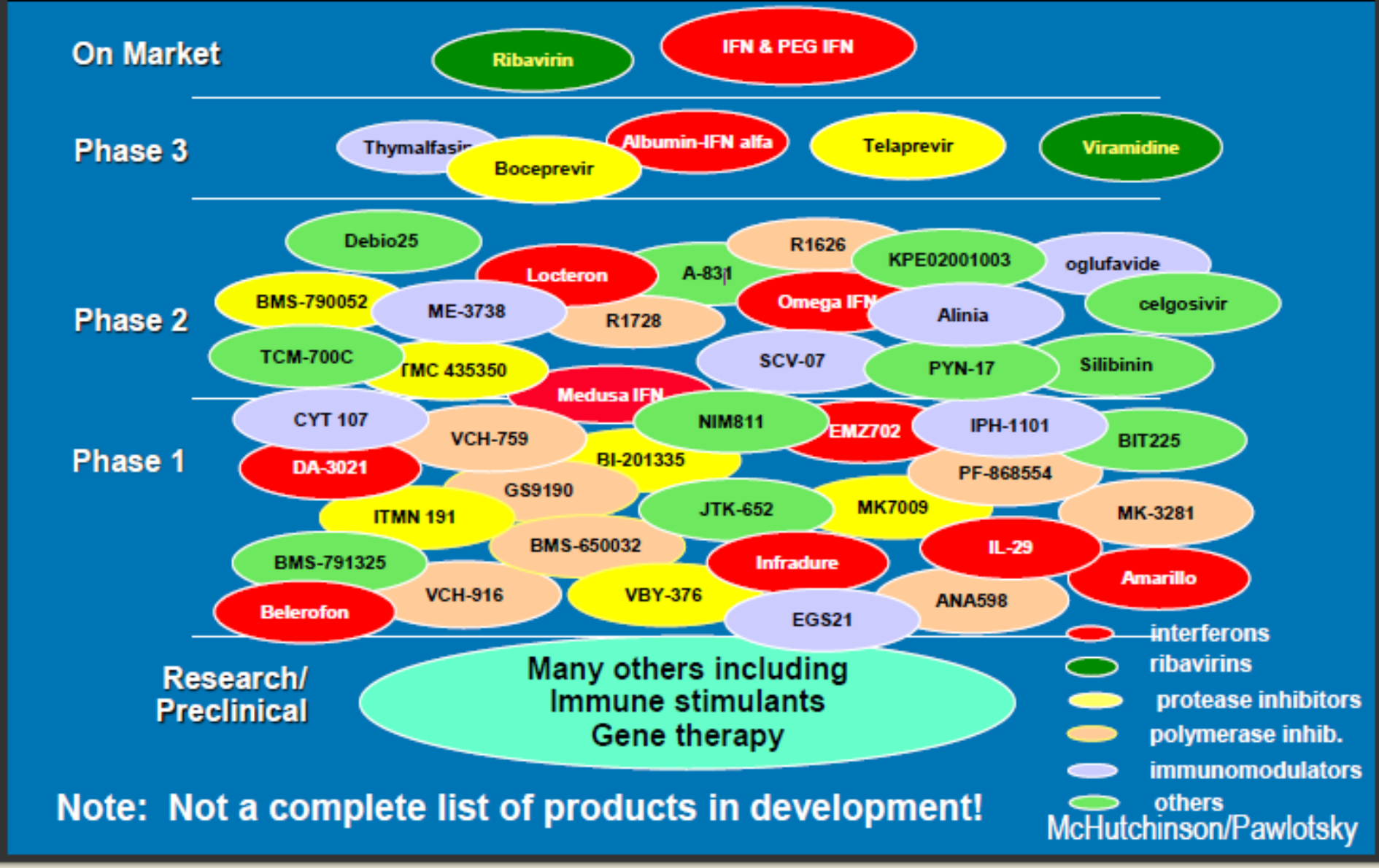
  Per cent of total cohort completed: 1.7%

Butt et al. Liver International 2010. On line before publication

Conclusions: Large Barriers to Treatment of HCV in Developed Nations

- Access to care in US
- Able to afford treatment in US
- Eligible for treatment (25%-50%)
- Eligible and want treatment (5%-15%)
- Finish treatment (25%-70%)
- Treated and get cured (~50%)

Hepatitis C Drug Development: 2008



Note: Not a complete list of products in development!

McHutchinson/Pawlotsky

Alaska Hepatitis C Program Strategy for Treatment Selection: 2010-2015

- 2010: Treat persons with HCV genotypes 2 & 3 and selected persons with genotype 1 with advanced fibrosis
- 2010-2013: Treat person with genotype 1 with grade 3-4 fibrosis with Peg-IFN, RBV + Protease Inhibitor
- 2014-2015 and beyond: Treat all eligible patients with all oral IFN-free regimen