



# VIRAL HEPATITIS IN THE ARCTIC – ON THE EDGE OF EXTINCTION

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Arctic viral hepatitis working group since 2006 with experts from the circumpolar area.

Thanks to

- Brian McMahon, Alaska ,
- Anders Koch,
- Vladimir Chulanov, Russia,
- Gerry Minuk, Canada
  - for sharing data and slides

- Nothing to disclose

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## Viral hepatitis in the Arctic What matters?



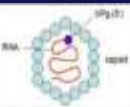
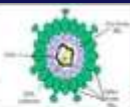
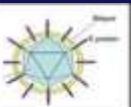
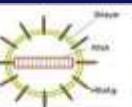

- Hepatitis A and vaccination against hepatitis A
- Hepatitis E
- Hepatitis B
  - Among children
  - Vaccination strategies
  - Risk of cancer
  - Genotypes
- Hepatitis D

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## The hepatitis viruses

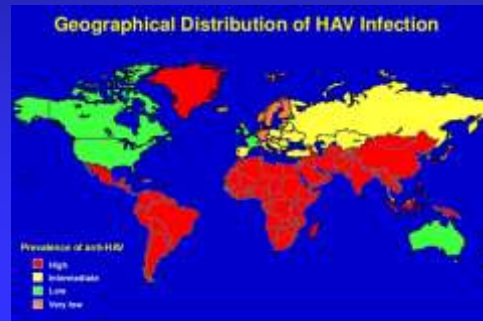
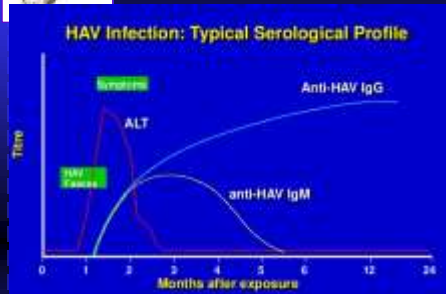


					
<b>Name of Virus</b>	Hepatitis A Virus (HAV)	Hepatitis B Virus (HBV)	Hepatitis C Virus (HCV)	Hepatitis D Virus (HDV)	Hepatitis E Virus (HEV)
<b>Classification</b>	Picornavirus	Hepadnavirus	Flavivirus	Deltavirus	Hepevirus
<b>Viral genome</b>	ssRNA	dsDNA	ssRNA	-ssRNA (-ve)	ssRNA
<b>Transmission</b>	Enteric	Parental	Parental	Parental	Enteric
<b>Incubation period</b>	15-45 days	45-160 days	15-150 days	30-60 days	15-60 days
<b>Chronic Hepatitis</b>	No.	Yes. 10% chance	Yes. >50% chance	Yes. <5% of coinfectious >80% of superinfectious	No.
<b>Cure?</b>	No cure. Treatments usually tackle the symptoms.	No cure. Treatments usually tackle the symptoms.	Cure rate around 50%	No cure. Treatment: Alpha interferon for 12 months.	No cure. Treatments usually tackle the symptoms.

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## Hepatitis A



## Hepatitis A



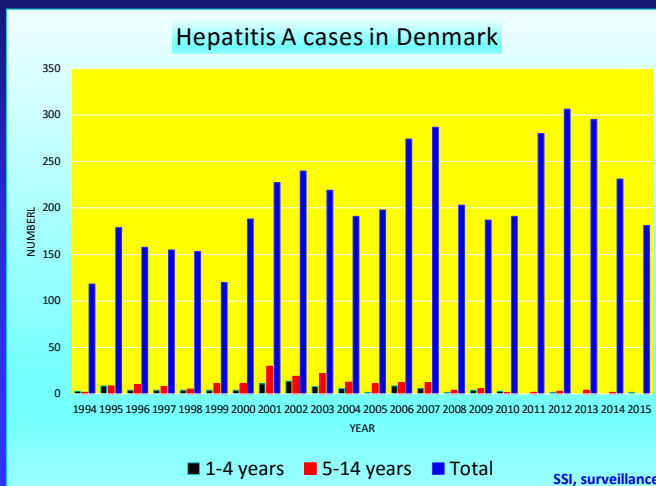
- Is endemic with epidemics in the majority of the world
- In the Arctic we saw an epidemic pattern
- In children aged <6 years, 70% of infections are asymptomatic. If illness, < 30% with jaundice
- Among older children and adults, infection is typically symptomatic, with jaundice occurring in >70% of patients.
- Can be prevented by vaccination. Most part of the world a 2-dose schedule after 12 month of age
- Vaccination at a younger age less immunogenic
- Vaccination probably lifelong protection
- Universal HAV vaccination in Alaska, but not in Russia, Greenland and Canada



## Hepatitis A (HAV)



- Denmark Incidens 2013: 1.8/100.000 PYRS



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## HAV epidemics in Greenland



- 1970-74
  - 11/15 districts
  - 4,961 cases (11%) of clinical hepatitis
  - Incidence: 2,606/100.000 persons per year
  - 93% of cases among persons aged 0-25 years
  - Immunity in older persons compatible with 1947-48 epidemic
  - Attack rate Danes: 1/6 AR for Greenlanders
  - Case-fatality rate 0.3%

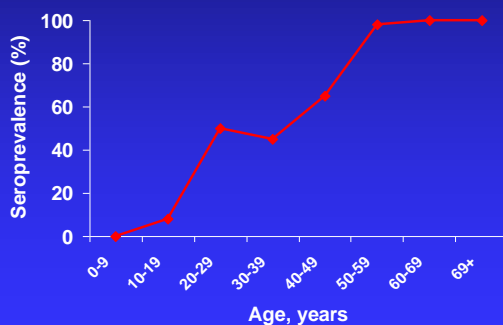
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## HAV antibodies at present in Greenland



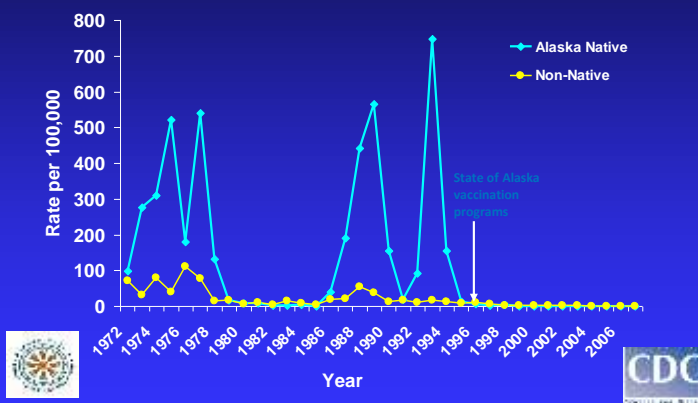
HAV antibodies  
Sisimiut & Ilulissat 1994 (Langer et al).



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## Hepatitis A in Alaska Natives and Non-Natives in Alaska, by Year



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## Hepatitis A in Children in Alaska and the Arctic



- All children in Alaska regardless of ethnicity have been given hepatitis A vaccine since 1997 (>< lower 48)
- Two long-term studies on Alaska Native children vaccinated ages 3-6 years and 6 months-15 months show >90% protection at 20 years and 15 years
- By 2014 the Arctic rated as low risk area by the WHO



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## Hepatitis E (HEV)



- Every year an estimated 20 million HEV infections occur globally resulting in more than 3 million cases and 70,000 deaths (Rein, 2012).
- Most cases occur in developing countries
- Hepatitis E case fatality is highest among pregnant women, which can be as high as 20% (3. trimester)

### Seroprevalence

- Worldwide 1-50%, (highest South Asia, North Africa)
- Denmark 1983 (31.6%), 2003: (20%), farmers : 51%  
(Christensen, 2008)
- Greenland : 3% seroprevalence (~rate of false test positivity)  
(Langer et al 1994)

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## Hepatitis B epidemiology



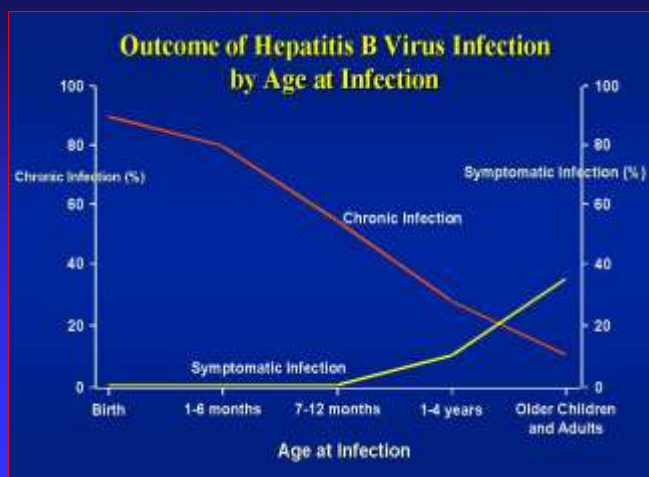
- About 2 million have markers of exposure to HBV (HBcAb+)
- Every year around 4 million new cases of HBV infection
- 4000 million chronic carriers
- Mortality: 1 million/yr
- Can be prevented with vaccination



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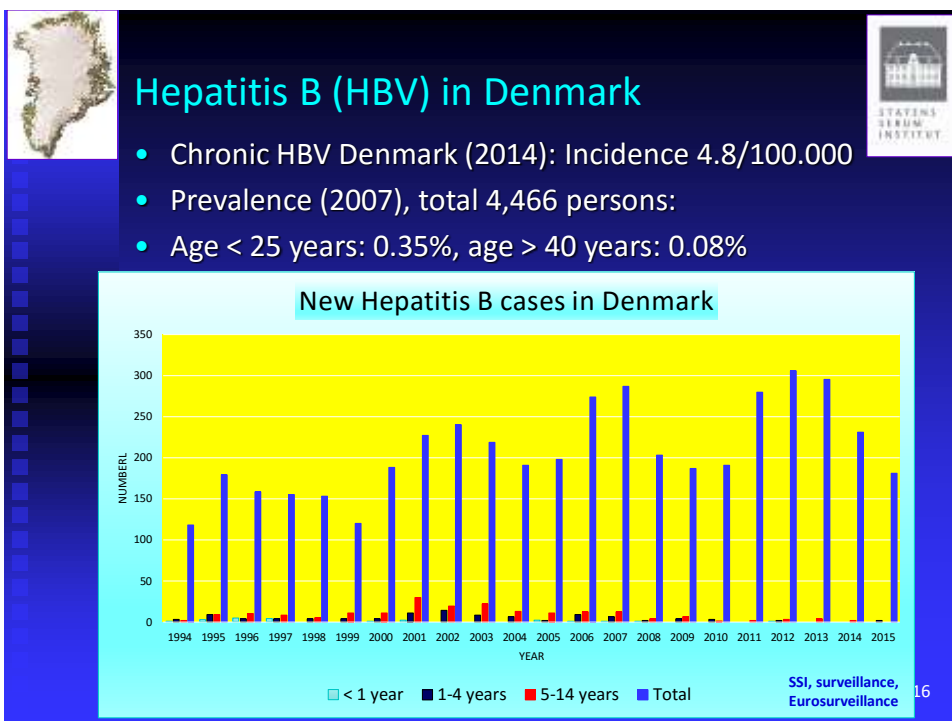
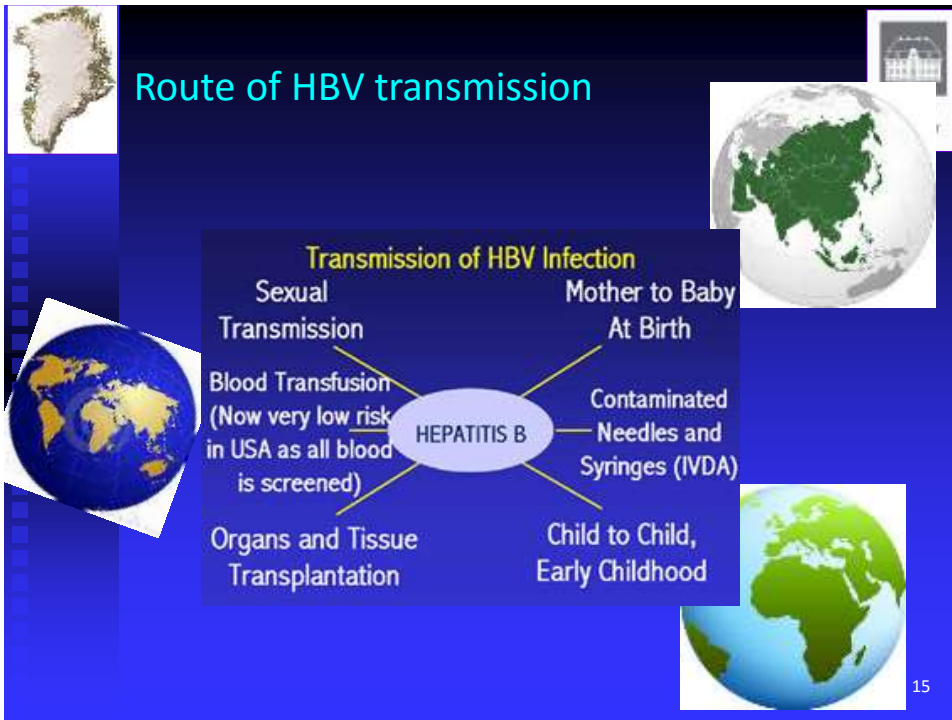


## HBV - Risk of chronic infection by age at infection



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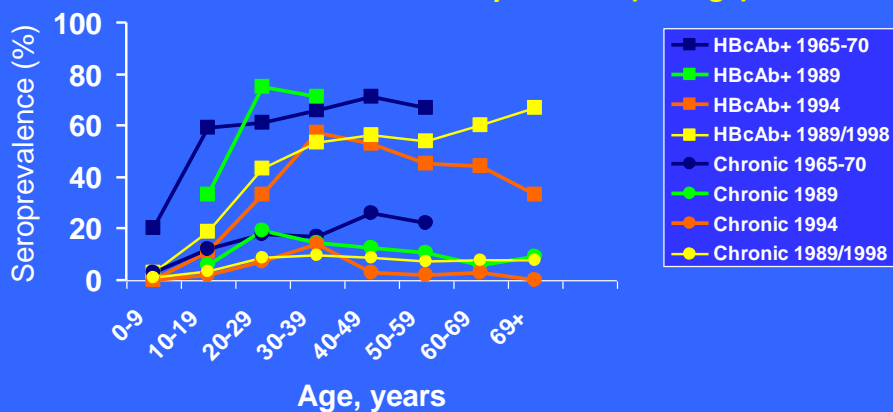




## Greenland HBV Markers by age 1965-1998



40 – 75% exposed (HBcAb+)  
7 – 20% chronically infected (HBsAg+)

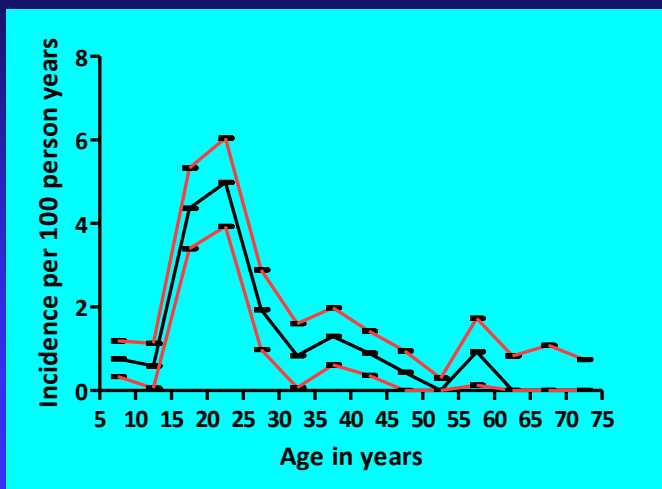


Based on studies by Skinhøj (1974), Olsen OR (1989), Langer (1997) and Børresen (2011)

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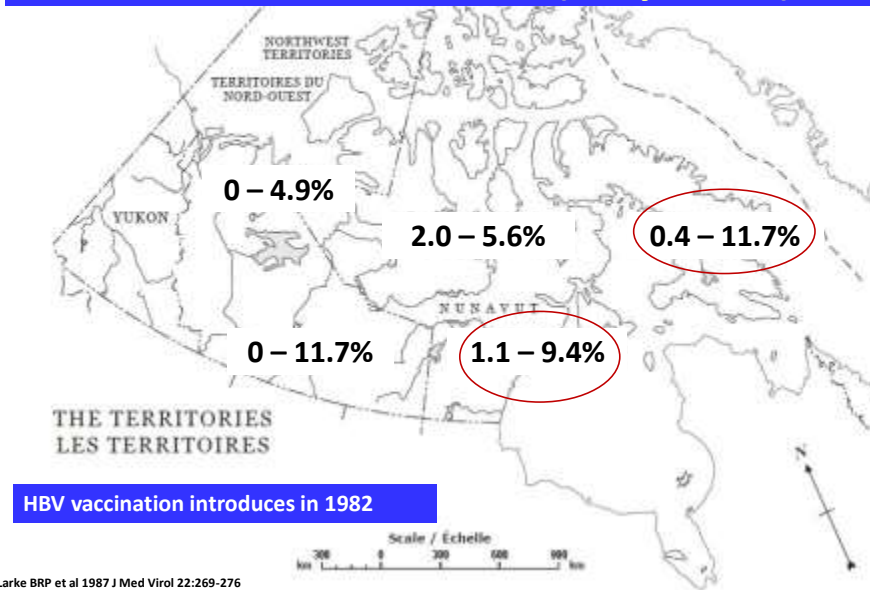


## Hepatitis B incidence Greenland



(Børresen, 2015)<sup>18</sup>

## Prevalence of chronic HBV in the Northwest Territories and Nunavut (early 1980's)



Larke BRP et al 1987 J Med Virol 22:269-276



## Hepatitis B in Alaska

- 1972-73: High incidence acute HBV
- 1973-1974: Serosurvey found prevalence of HBsAg in 12 villages in Southwest AK 6.4% (0- 20.1%)<sup>1</sup>
  - 1974-1978: Incidence study 1280 seronegative persons: 14.8% HBV (2)
  - 29% infected < 5 years of age 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)

<sup>1</sup>Schreeder Am J Epidemiol 1983; 118:543-9

<sup>2</sup>McMahon JID 1985; 151:599-603



## HBV In Alaska

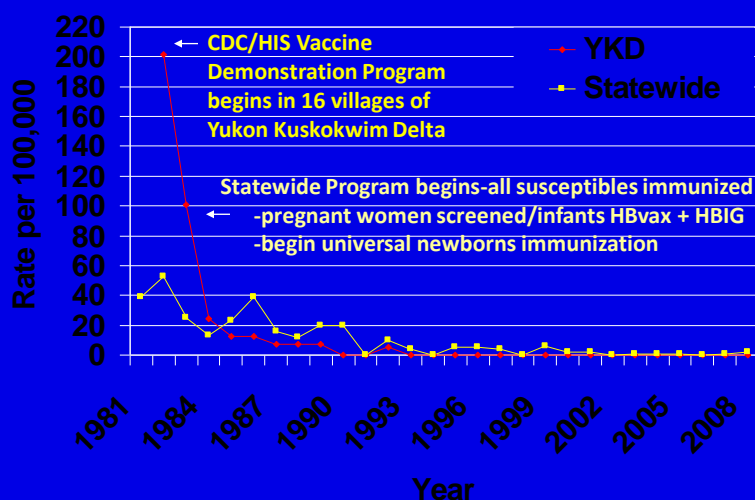


- From 1983-1987, 52,000 Alaska Native Persons were tested for hepatitis B seromarkers and 40,000 with negative markers were vaccinated
- (3.1% HBsAg pos, 1536 included for follow-up).
  - 657 children < age 20 with chronic hepatitis B virus (HBV) infection were identified
  - All identified persons have been followed prospective since then (median f/u 25 years)
  - All newborns since have received hepatitis B vaccine starting at birth (0,1,12 month)
    - Children of HBsAg-positive mothers also receive HBIG at birth

McMahon et al



## Incidence Symptomatic HBV in Alaska Native Peoples 1981- 2008



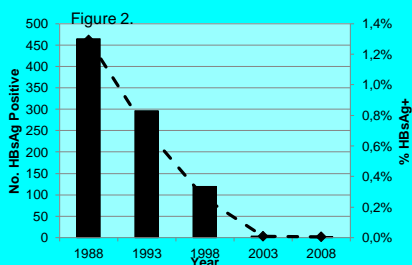
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## HBV In Alaska



### Number of HBsAg-positive Alaska Native (AN) Children Under 20 Years of Age: 1988-2008



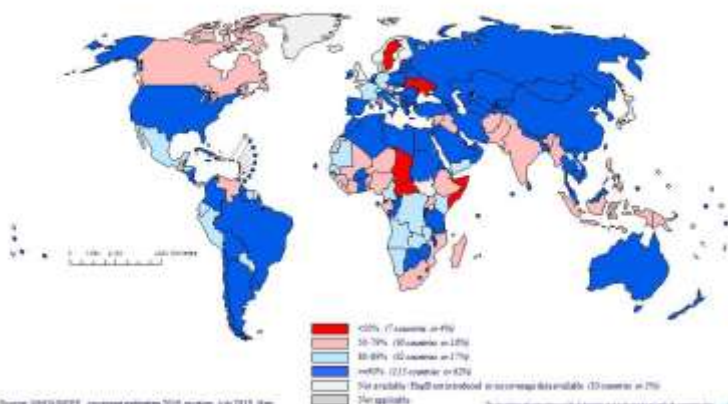
Prevalence of HBsAg in 20,657 persons <20 years screened 1983-1987 was 3.2%. In 2012, no AN children are known to be HBsAg+



## Hepatitis B Vaccine Coverage



### Immunization coverage with 3rd dose of HepB vaccines in infants, 2014



Source: WHO/UNICEF coverage estimates 2014, version 1.0, July 2015. Map production: Immunization Vaccines and Biologicals (VBI), World Health Organization. Date created: 18 July 2015.

The immunization coverage estimates are based on data from the most recent available survey. The coverage estimates are based on data from the most recent available survey. The coverage estimates are based on data from the most recent available survey. The coverage estimates are based on data from the most recent available survey.

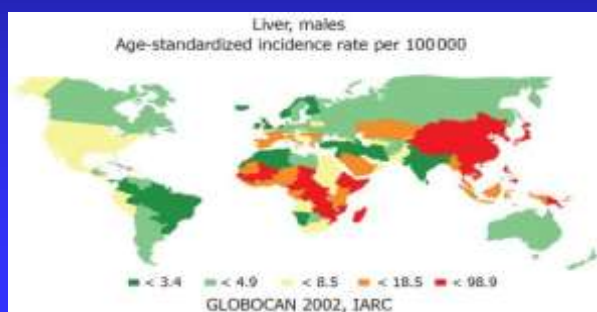
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## Lifetime Risk of Hepatocellular Carcinoma (HCC)



- Hepatitis B (HBV): lifetime risk of HCC: 1%-25%
- Rates of Hepatocellular carcinoma (HCC) are different within Arctic populations



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## HCC Inuit 1969-88, 1989-97,



Area	ASR 1969- 88	ASR 1989- 98	SIR (95% CI) Connecticut	SIR (95% CI) Denmark	SIR (95% CI) Canada
Circumpolar	8.0		4.0 (3.0-5.2)	3.1 (2.2-4.3)	4.1 (3.0-5.3)
Alaska	15.1	17 ♂ 12 ♀	7.2 (5.1-9.9)	5.5 (3.9-7.6)	7.7 (5.2-10.2)
Greenland	5.7	8 ♂ 2.9 ♀	2.7 (1.5-4.5)	2.1 (1.2-3.4)	2.8 (1.5-4.5)
Canada	1.0	4.4	0.4 (0.0-2.2)	0.3 0.0-1.7	0.4 0.0-2.1

Based on Friberg, Storm, Børresen and McMahon

ASR Age Standardized rates, SIR Standard Incidence ratios

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## Different incidence of HCC within the Arctic



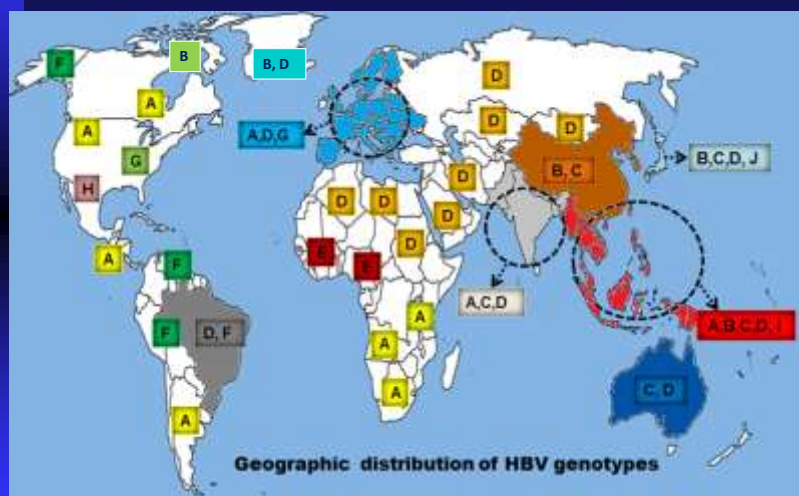
HBV - Risk of chronic infection and risk of HCC

- Host:
  - Age at infection
  - Area of origin
  - Sex (male)
  - Co- infection with HIV, HDV,
  - Aflatoxin
- Virus:
  - Genotype (A-H)
  - Viral load, HBeAg positivity
  - Mutations

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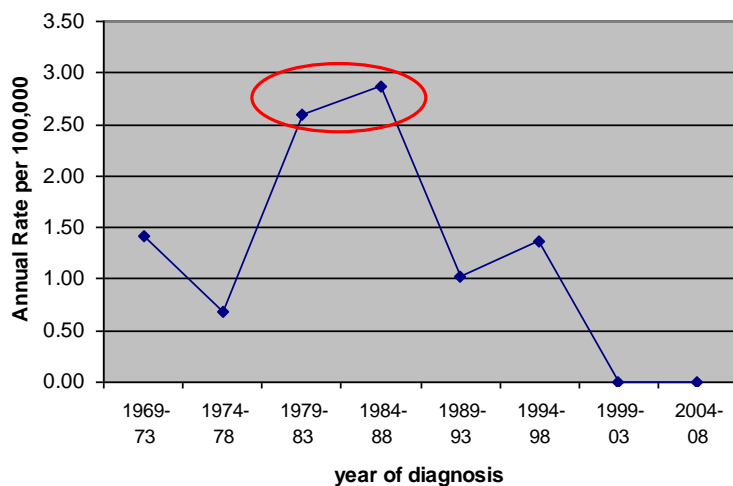
## HBV – Genotype (A-H)



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### HCC in Alaska Natives <20 years of age



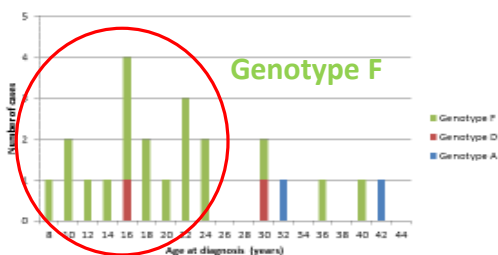
P value for trend = 0.002

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### Alaska Genotype F

#### Number of Cases of HCC Occurring in Young Persons by Age and HBV Genotype\*



\*No cases occurred in persons infected with HBV genotypes B6 or C

McMahon et al, unpublished data





## Genotype distribution in the Arctic (%)



	Alaska <sup>1</sup> 1196 HBsAg+ N=100	Greenland <sup>2</sup> 415 HBsAg+ N=100	Greenland <sup>3</sup> N=52
A	13	24	-
B	4	15	91
C	7	1	-
D	56	60	9
E	-	-	-
F	20	-	-

1. MMahon et al. 2014

2. Børresen et al. 2012

3. Krarup et al. 2004

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## Questions raised



- HBV genotype distribution different in Alaska and Greenland
  - F frequent in Alaska, not in Greenland
  - B frequent in Greenland, not in Alaska
- Incidence of HCC high in Alaska, low in Greenland
- HBV genotypes related to morbidity in Alaska
  - F related to HCC in young persons
- What is the impact on genotype B on liver disease in the Arctic?

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## Worldwide - Two major subtypes of Hepatitis B virus genotype B



<b>Bj</b> (‘Japan’)	B1	Non-recombinant	Less commonly associated with HCC
<b>Ba</b> (‘Asia’)	B2	Intergenic recombination with HBV/C in core promoter/precore/-core genome region	Higher risk of HCC development in HBV carriers
	B3		
	B4		
	B5		

Sugachi et al. J Virol 2002  
Sakamoto et al. J Gen Virol 2006  
Sugauchi et al. Gastroenterology 2003  
Kao et al. Gastroenterology 2000  
Orito et al. Hepatology 2001

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## Comparative study of HBV B subgenotypes in the Arctic 2007



- 50 HBV carriers
  - Alaska: 31
  - Canada (Baker lake): 8
  - Greenland (Sisimiut): 11
- All native persons
- No HCV or HIV coinfection
- Classification
  - Asymptomatic
  - Chronic liver disease
  - LC or HCC
- 20/50 HBV strains complete genome sequenced
  - 6 Alaska
  - 8 Canada
  - 6 Greenland
- All 50 HBV strains amplified in EnhII/Cp/preC/C regions
- Comparisons with bank HBV sequences from Asia

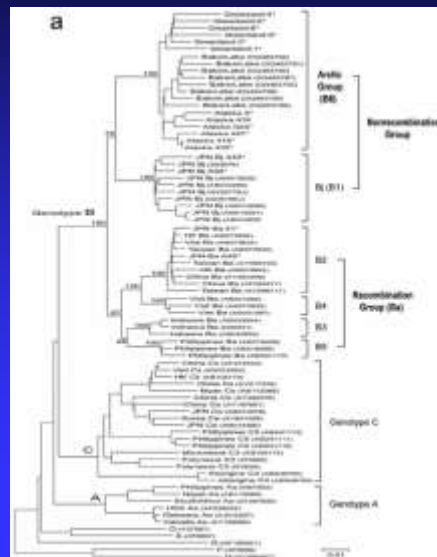
Sakamoto et al. J Inf Dis 2007; 196: 1487-34



## Phylogenesis based on complete genome sequences



- Asian/Japanese/Arctic HBV strains in 6 distinct clusters
- Asian/Japanese strains in known clusters Bj/B1 + Ba/B2-B5
- All Arctic strains in distinct separate (unclassified) cluster
- Suggested designation B6



## Morbidity and HBV B subgenotypes



Feature	HBV/B6 (n = 50)	HBV/Bj (n = 50)	HBV/Ba (n = 50)	P
Male sex	33 (66)	34 (68)	36 (72)	Matched
Age, mean ± SD, years	48.1 ± 19.6	48.1 ± 16.9	47.9 ± 13.1	Matched
Hepatitis B e antigen	6 (12)	8 (16)	20 (40) <sup>a</sup>	<.02
DNA >5 log copies/mL	9 (18%)	18 (36)	36 (72) <sup>b</sup>	<.001
Alanine transaminase	40.3 ± 36.3	43.1 ± 33.4	94.0 ± 94.1 <sup>c</sup>	<.001
Clinical state				
Asymptomatic	35 (61) <sup>d</sup>	22 (44)	15 (30)	<.02
Chronic hepatitis	15 (30)	24 (50)	21 (42)	NS
Liver cirrhosis/hepatocellular carcinoma	0	4 (8)	14 (28) <sup>e</sup>	<.03

**NOTE.** Data are no. (%) of participants, unless otherwise indicated. HBsAg, hepatitis B e antigen; NS, no significant difference.

<sup>a</sup> For B6 vs. Ba,  $P = .0026$ ; for Bj vs. Ba,  $P = .0143$ .

<sup>b</sup> For B6 vs. Ba,  $P < .0001$ ; for Bj vs. Ba,  $P = .0006$ .

<sup>c</sup> For B6 vs. Ba,  $P = .0006$ ; for Bj vs. Ba,  $P = .0005$ .

<sup>d</sup> For B6 vs. Ba,  $P = .0001$ ; for B6 vs. Bj,  $P = .0154$ .

<sup>e</sup> For B6 vs. Ba,  $P < .0001$ ; for Bj vs. Ba,  $P = .0214$ .



## Hypothesis: Co-existence of HBV B genotype and Eskimos



- Eskimos migrated from East Asia/Siberia to Alaska 10,000 BC
- Later developed into 3 groups
  - Aleutians (Aleuts, West Alaska)
  - Yupik (West Alaska)
  - Inuit (Point Barrow, Alaska, Canada & Greenland)
- The Inuit spread from Alaska eastwards 1,000 AD
- Subgenotype B6 followed the Eskimos from Asia?
  - Developed from B1?
  - Common forefather of B1/B6?



— HBV genotypes B1/B6  
— HBV genotype F

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## Hepatitis B – genotype B



- A new HBV/B subgenotype B6 identified
- All 50 Arctic HBV/B strains belonging to that subgenotype
- Related to the non-recombinant Japanese Bj/B1 subgenotype and different from recombinant Asian Ba/B2-B5 subgenotypes
- Non-recombinant B1 & B6 appear less virulent than B2-B5
- Classification of HBV/B into recombinant and non-recombinant forms
- B6 May have followed the Eskimos from Asia
- Larger studies on clinical manifestations of B6 needed

1. 38



## HBV in the Arctic



- HBV vaccination has eliminated new cases of HBV among children in Alaska
- Less long-term consequences than expected in Greenland as compared with Alaska – Different genotypes
- Infection in the 80és in Canada and Alaska among children, and in Greenland in teenage years
- New 'Arctic' B<sub>6</sub> sub-genotype identified, related to benign Japanese B<sub>1</sub> sub-genotype



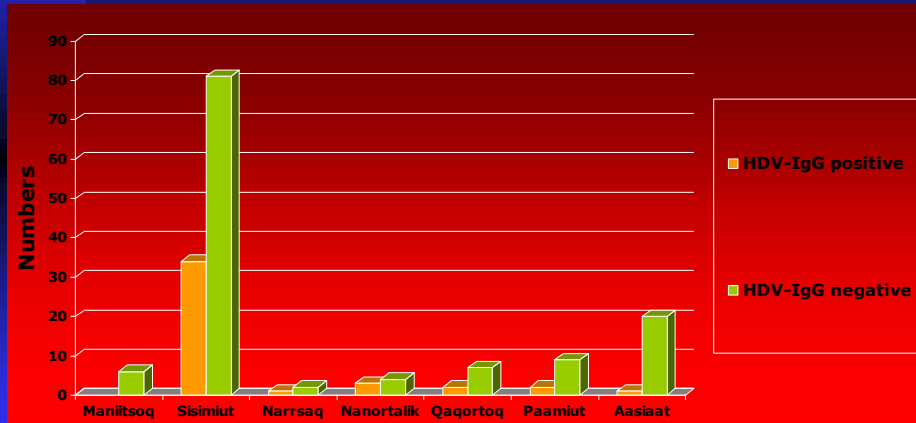
## Hepatitis D – delta virus



- Worldwide, 8 genotypes (clades), genotype I most adverse outcomes
- Presence of HBV-DNA and HDV-RNA is associated with a lower HBV remission rate
- Super-infection with HDV has a higher risk of chronicity and worse long term outcome than HDV co-infection
- Hepatitis D is only present i Greenland and Chukotka in Russia in the Arctic
- However different genotypes (I in Greenland, II in Chukotka)
- Does Hepatitis D matter?



## Greenland HDV by area

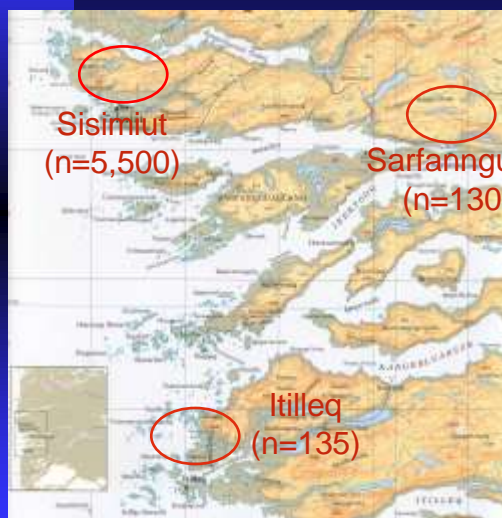


Børresen et al. 2012

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## Hepatitis B and D outbreak in Itilleq near Sisimiut in Greenland



Børresen et al., Journal of Viral  
Hepatitis, 2009,

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## Severity markers for HBsAg-positive, 2006-2007



	Children (n=15) (%)	Adults (n=16) (%)
<b>ALT &gt; 45 I/U</b>	<b>73</b>	<b>38</b>
Viral load > 1 mio. IU/mL	47	6
HBeAg positive	53	0
Hepatitis D (HDV) positive	40	63
<b>HDV-seroconversion</b>	<b>33</b>	<b>0</b>

### Regression model:

Hepatitis D the strongest predictor for elevated ALT (liver damage)

In 2009, additional 2 children HDV seroconverted

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## HBV in Itilleq – Conclusions



- High prevalence of chronic HBV infection, especially among children (genotype D)
- Elevated liver enzymes in chronic infected (HBeAg-positive) children
- Super-infection with Hepatitis D most likely, (clade I)
- Ongoing HDV outbreak in Itilleq

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## Viral hepatitis – On the edge of extinction?



- Hepatitis A By 2014 the Arctic rates as low risk country.
- Vaccination against hepatitis A and B in parts of the Arctic is a real success story.
- Hepatitis B – In Alaska the prevalence of HBsAg in Children has been reduces to 0
- Genotype F in Alaska sucks – but is dying out
- New 'Arctic' B<sub>6</sub> sub-genotype identified, related to benign Japanese B<sub>1</sub> sub-genotype
- Outbreak of Hepatitis D in Greenland - is HDV a treat?
- Hepatitis B introduced in the universal childhood vaccination programme In Greenland in 2010

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Tak for opmærksomheden

