HBV Vaccination Effectiveness in Greenland

Malene Landbo Børresen, MD. PhD
Dept. of Epidemiology Research, SSI
Dept. of Paediatric, Hvidovre Hospital

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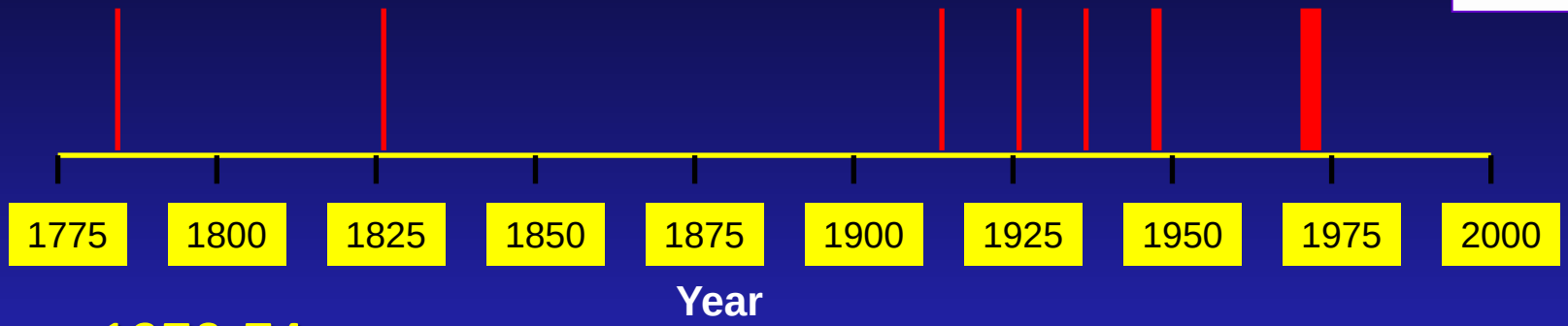
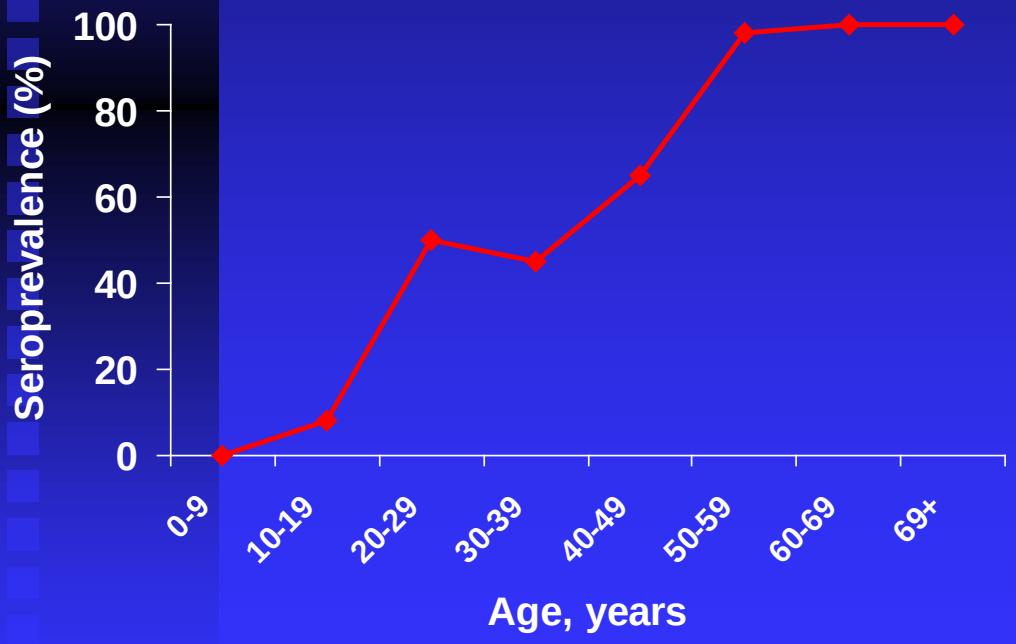
HAV EPIDEMICS



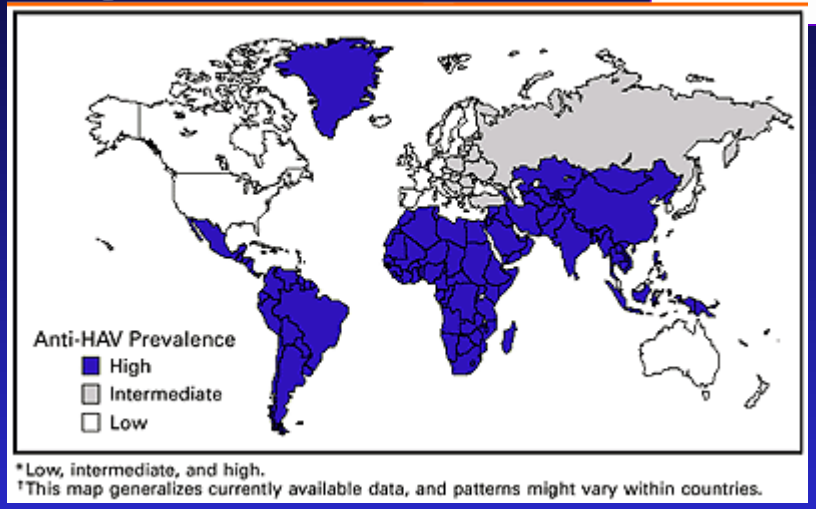
- 1970-74
  - 11/15 districts
  - 4,961 cases (11%) of clinical hepatitis
  - Incidence: 2,606/100.000 persons per year
  - 93% of cases among persons aged 0-25 years
  - Immunity in older persons compatible with 1947-48 epidemic
  - Attack rate Danes: 1/6 AR for Greenlanders
  - Case-fatality rate 0.3%

HAV AT PRESENT

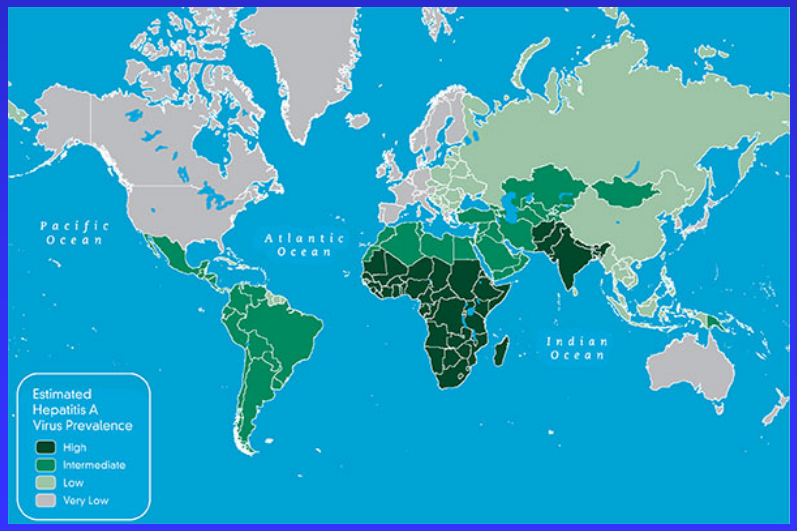
HAV antibodies
Sisimiut & Ilulissat 1994 (Langer et al).



HAV antibodies



Estimated HAV prevalence

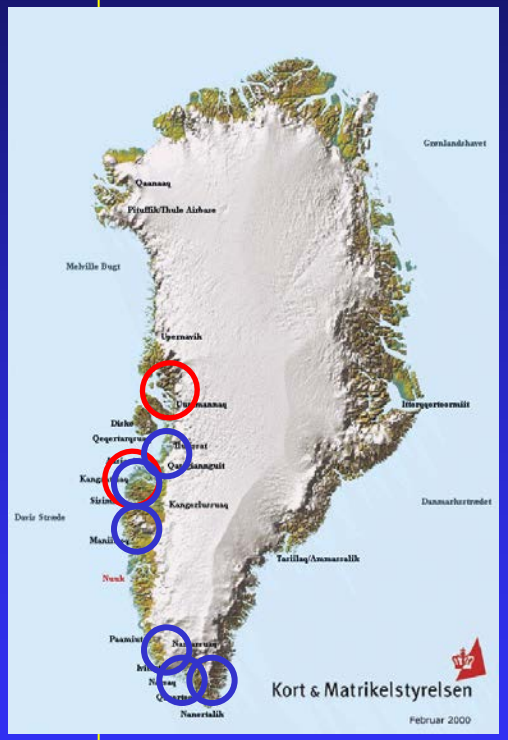


HCV, HDV, HEV

- HCV, Langer et al 1994
  - 0.8% seroprevalence
  - None HCV RNA positive
- 0.09% in routine tests

- HDV
  - 11% (1989, Olsen), 40% (1994, Langer), 30% (2009, Børresen) of HBsAg-infected HDV positive

- HEV, Langer et al 1994
  - 3% seroprevalence (~rate of false test positivity)
  - None HEV RNA positive



Hepatitis B Vaccine Coverage

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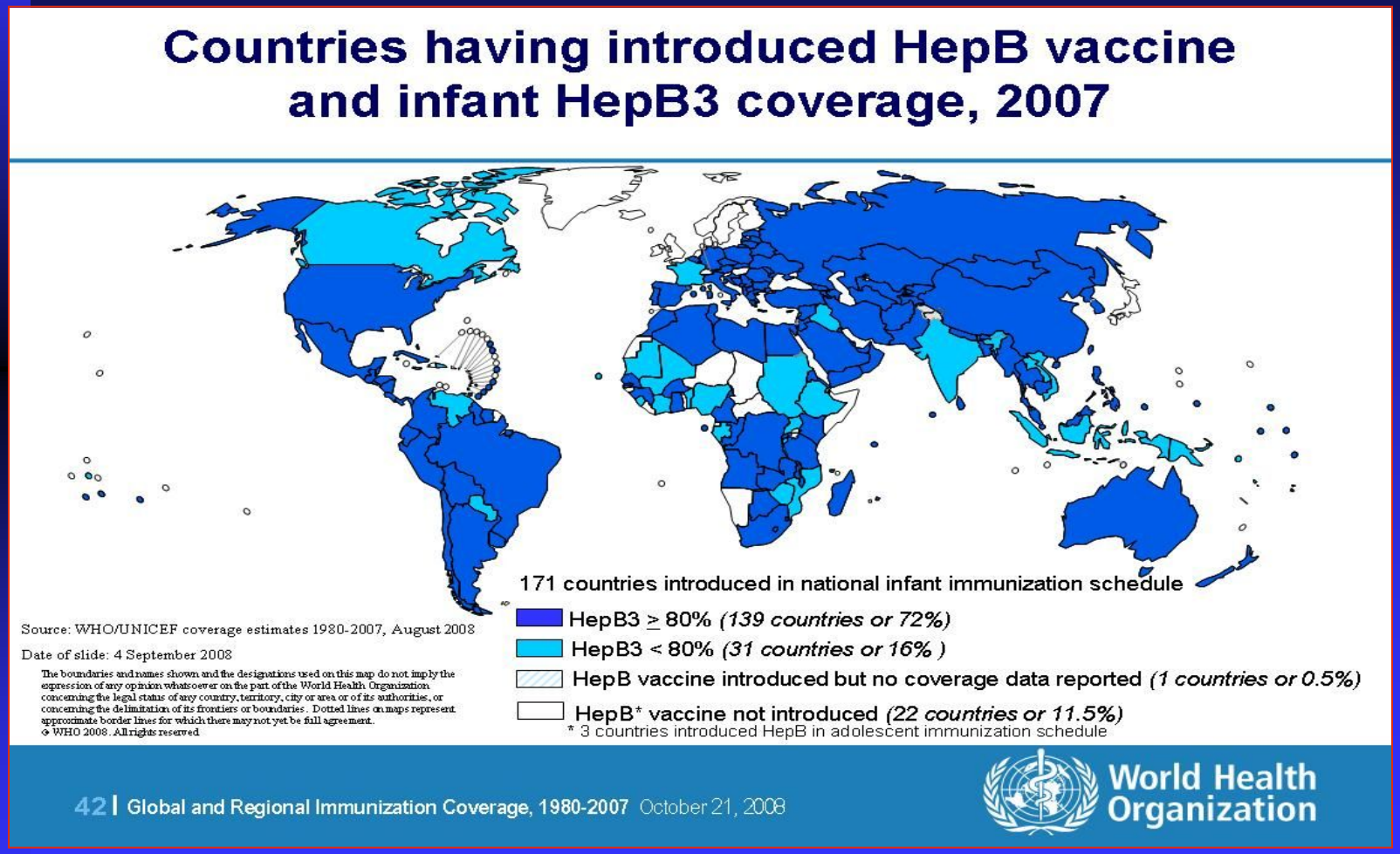

By september, 2010 the HBV vaccine was included in the childhood vaccination program in Greenland

HBV screening of pregnant women in Greenland

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Established in 1992

- HBsAg testing at first pregnancy examination
- Test result and date of testing recorded on the perinatal chart
- Children born to HBsAg positive mothers should be vaccinated according to National Guidelines

Children born to HBsAg-positive mothers

Birthday 1 Month **2 Month** **12 Month**

1. Hep B 2. Hep B
+ immunoglobulin

3. Hep B

4. Hep B

HBV vaccine: 10 mikrogram recombinant

Aims of the study

Part I

- HBsAg prevalence among pregnant women

Part II

- Vaccination coverage and timeliness of given vaccinations among children of HBsAg-positive mothers
- Prevalence of break-through infections among vaccinated children of HBsAg-positive mothers
- Levels of protective antibodies among vaccinated HBV-negative children.

Børresen ML, Koch A, Biggar RJ, Ladefoged K, Melbye M, Wohlfahrt J, Krause TG.
Am J Public Health. 2012 Feb;102(2):277-84.

Materials and Methods

Hepatitis B database

- Established in 2004
- All HBV test results (HBsAg and anti-HBs) from Greenland from 1992 to 2009, 2000-2004 missing due to errors in the database under construction

CRS – Civil Registration System

- Identifying children born in Greenland from 1992 to 2007

Linkage by the mothers CRS-number, children born to HBsAg-positive mothers identified

HBV prevalence and vaccination coverage – methods and result

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4050 pregnant women with HBV test results

3.2% (135) HBsAg-positive regional differences

Gave birth to **279** children1992-2007

31 children excluded due to dead, emigration, mother HBsAg-negative during current pregnancy

248 children included

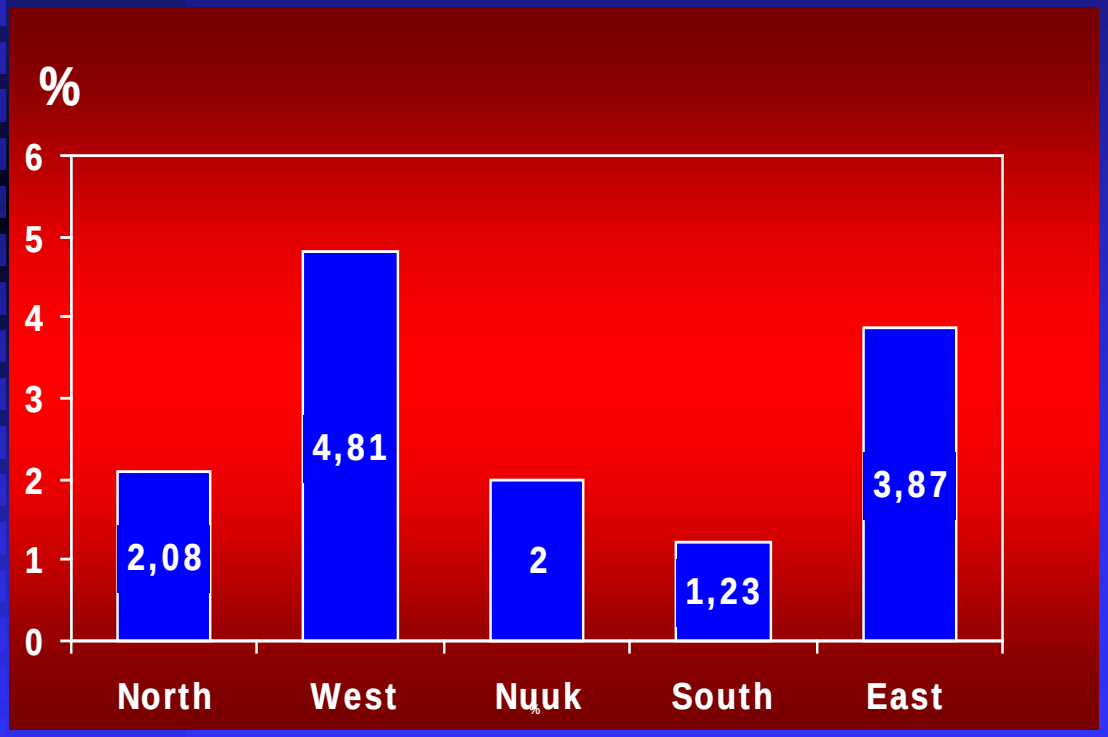
Review of perinatal chart:
Immunoglobulin and 1. vaccination

Medical and vaccination chart:
(1.) 2. til 4. vaccination

207 (83%) children with information on vaccination coverage

HBsAg positive mothers by area (birthplace of child)

4050 women. HBsAg prevalence at first pregnancy after 1992



P < 0.001

Vaccination coverage for 207 children from 1992 to 2007

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	Children n.	No vac.	1. vac.	2. vac.	3. vac.	4. Vac.
Overall	207	**42 (20.3%)**	24 (11.6%)	21 (10.1%)	50 (24.2%)	**70 (33.8%)**
Vaccination "on time"[a]	165		143/165 (87.2%)	110/141 (78%)	67/120 (55,8%)	64/70 (91.4%)
Birth period						
1992-1995	79	20 (25.3%)	11 (13.9%)	12 (15.2%)	25 (31.7%)	11 (13.9%)
1996-2000	88	11 (12.5%)	10 (11.4%)	6 (6.8%)	14 (15.9%)	**47 (53.4%)**
2001-2007	40	11 (27.5%)	3 (7.5%)	3 (7.5%)	11 (27.5%)	**12 (30%)[b]**
Area						
High-Endemic	163	34 (20.9%)	22 (13.5%)	14 (8.6%)	35 (21.5%)	58 (35.6%)
Low-Endemic	44	8 (18.2%)	2 (4.6%)	7 (15.9%)	15 (34.1%)	12 (27.3%)

[a] 48 hours, 2 months, 4 months, 18 months, b $p < 0.001$, HBIG 131/165 (79.4%)

Follow-up study 2008/2009

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248 children candidates for follow-up study

→ 35 excluded
dead (n=5),
emigrated (n=8)
excluded areas (n=24)

↓

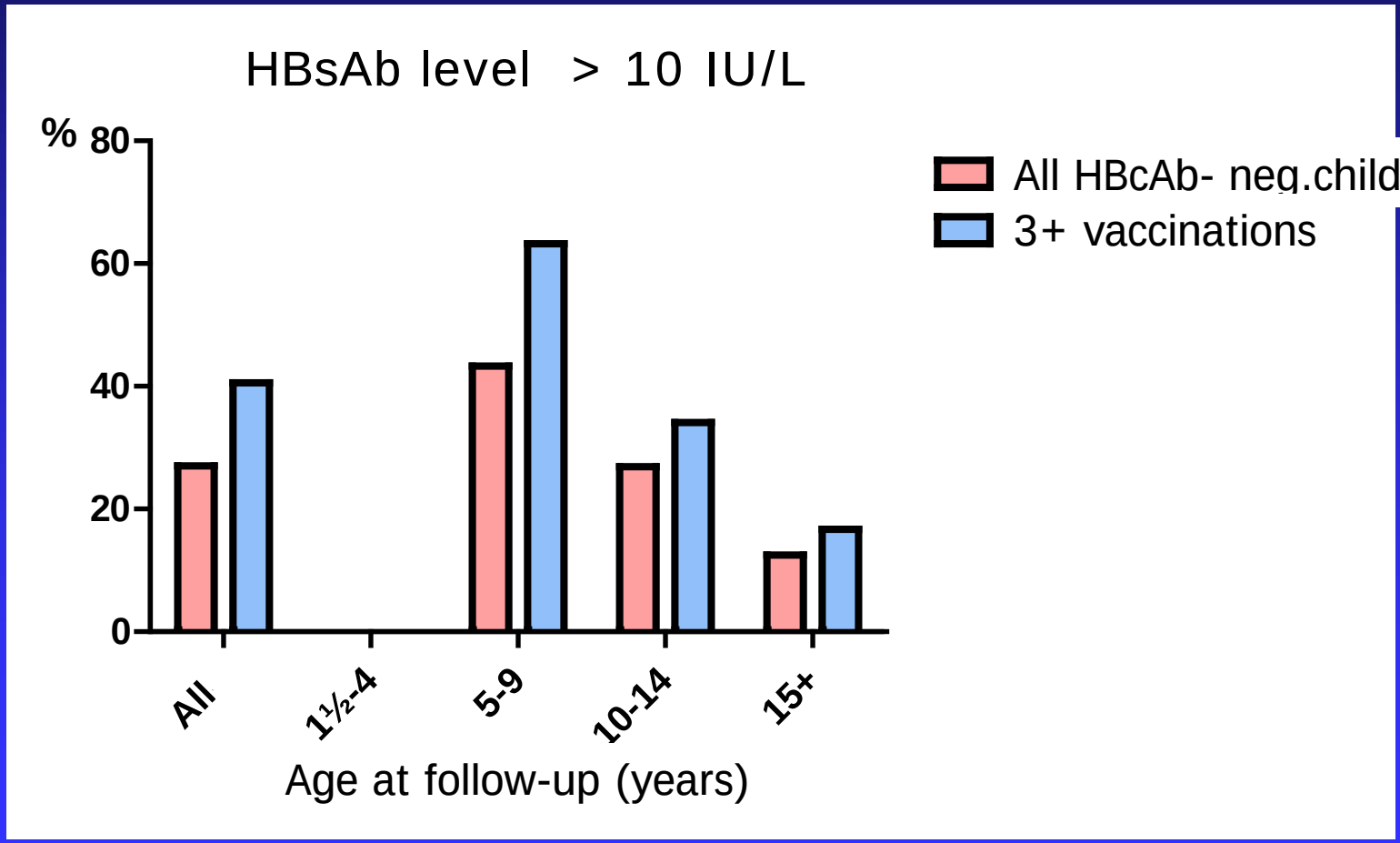
213 children invited for follow-up

↓

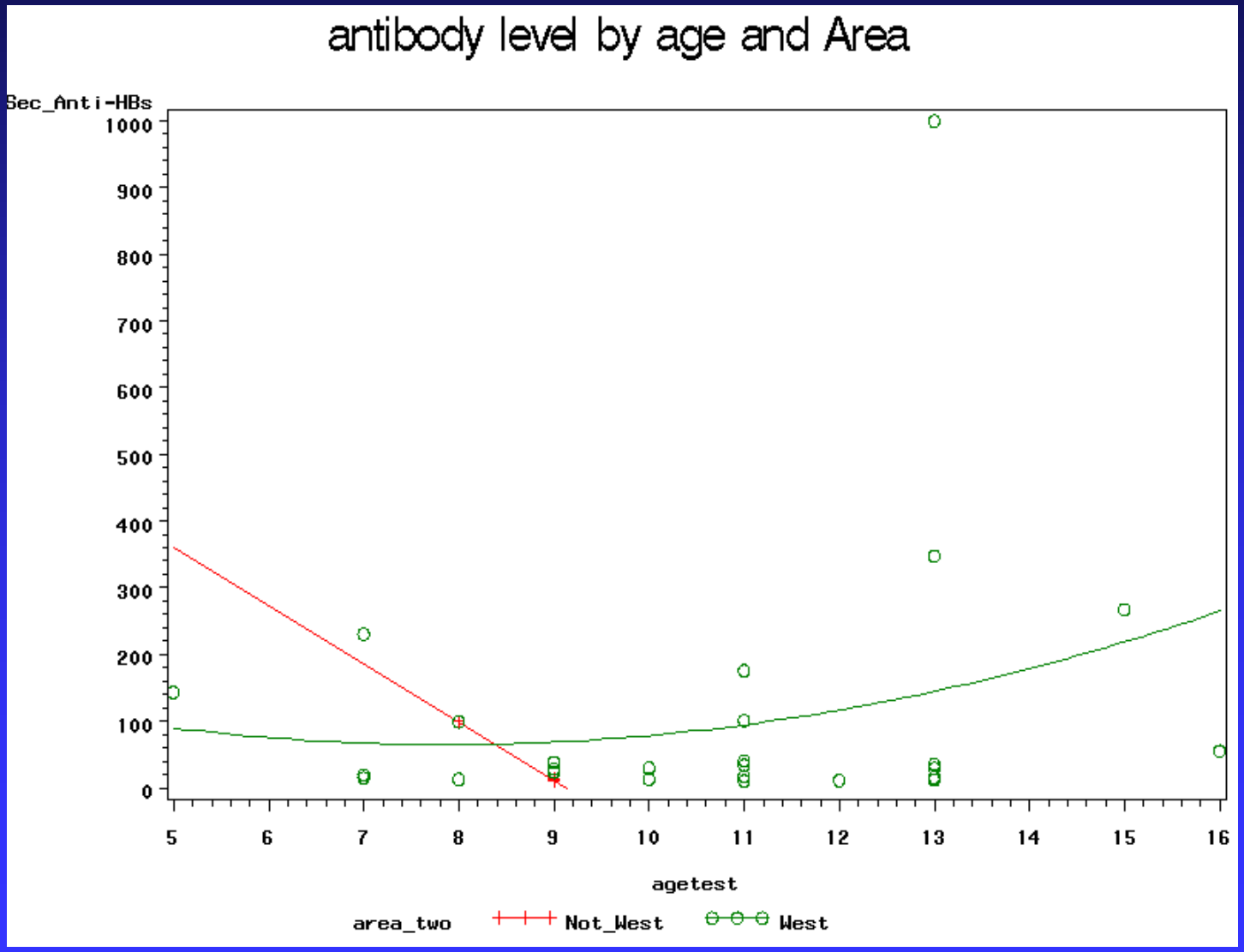
140 children (66%) HBV tested in 2008/2009

→ **3% (4) chronic carriers***
3% (4) immune *
94% (132) negative

HBsAb level >10 IU/L among 'at-risk' children by age group



HBcAb-negative children with 3+ vaccinations



Conclusions I

- Regional difference in HBV prevalence among pregnant women
- Every fifth child born to HBsAg positive mother received no immunoglobulin or vaccination postnatally
- Only every third received full vaccination program (4 vaccinations)
- 6 % (8) of ’at-risk children’ had break-through infections
- 50 % of these were HBsAg-positive
- Of the 8 HBcAb positive children, 7 had received at least 3 HBV vaccinations, but only half of them immunoglobulin

Conclusions II

- 59% of HBcAb-negative children with 3+ vaccinations had HBsAb < 10 IU/l
- 73% of all included children had HBsAb < 10 IU/L
  - NON – RESPONDERS?
  - COLD CHAIN?

- There was no expected fall in HBsAb level with time since vaccinations in the Western part of Greenland
- Older children with HBsAb > 100 IU/L
  - NATURAL BOOSTING

Does the cellular immune system work eventhough we found low HBsAb levels?

Perspectives

- The program did not work!
- Sep. 2010, HBV vaccination was included in the Childhood Vaccination Program in Greenland (birth, 3 month, 5 month and 12 month)
- HBV testing of pregnant women and HBIG continues
- Better information to the HBsAg-positive mothers as well as the health care personnel
- HBsAb level measurement of vaccinated infants of HBsAg-positive mothers at 15 month of age.
- Booster later in life..

On-going studies

Children with break-through infections

- Looking at escape mutations in the a-determinant of the s-gene

Vaccinated HBcAb-negative children

- Proposal to look at correlation between the HBsAb level and perfluorinated compounds (PCF)

Thank you for your attention

Mlb@ssi.dk

HBV vaccination breakthrough infections

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GL8 Mother of Family 4

not vaccinated

1527 ♀
Born 1998
FAMILY 1 (GL9)
- HBsAg +
- HBV DNA: 9.3×10^7 IU/ml
- ALT: 56
- HDV:neg

88 clones

Label 3:133 ♀
Born 1999
FAMILY 1 (GL15)
- HBsAg +
- HBV DNA: 2.8×10^7 IU/ml
- HDV:pos in '09

3 siblings having vaccine breakthrough

5192 ♂ Born 1993
FAMILY 4
- HBsAg+, anti-HBe+
- ALT: 358
- HDV: pos

*Stop mutant present at pos 216

5193 ♀ Born 1994
FAMILY 4 (GL4)
- HBsAg+, HBeAg+
- HBV DNA: 5.1×10^7 IU/ml
- ALT: 357
- HDV:pos

79 clones

*Stop mutant present at low level (3%)

*Stop mutant present at high level (70%) at pos. 69

Mutant also found in 2623, from Kangaatsiaq

5185 ♂ Born 2003
FAMILY 4
- HBsAg+, HBeAg+
- ALT: 321
- HDV:pos

93 clones

not vaccinated

1529 ♂
Born 1996
FAMILY 3 (GL6)
- HBsAg +
- HBV DNA: 5.0×10^7 IU/ml
- ALT: 54
- HDV:neg

56 clones

Label 3:10 ♀
Born 1990
FAMILY 3 (GL3)
- HBsAg +
- HBV DNA: 1.5×10^7 IU/ml
- ALT: 253
- HDV:pos

MENITSGFLGPLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGG
TTVCLGQNSQSPTSNHSPTSCPPTC*PGYRWMCLRRFIIFLFIL
LLCLIFLLVLLDYQGMLPVCPLIPGSSTTSTGPCRTCTTPAQGT
SMYPSCCCTKPSDGNCTCIPIPSSWAFGKFLWEWASARFSW
LSLLVPFVQWFVGLSPTVWLSVIWMMWYWGPSLYSILSPFLP
LL*PIFFCLWVYI. **(F8L, G44E, Y134F)**

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1527 ♀ Born 1998
- HBsAg +
- HBV DNA: 9.3×10^7 IU/ml
- ALT: 56
- HDV:neg

5192 ♂ Born 1993
- HBsAg+, anti-HBe+
- ALT: 358
- HDV: pos

5193 ♀ Born 1994
- HBsAg+, HBeAg+
- HBV DNA: 5.1×10^7 IU/ml
- ALT: 357
- HDV:pos

5185 ♂ Born 2003
- HBsAg+, HBeAg+
- ALT: 321
- HDV:pos

1529 ♂ Born 1996
- HBsAg +
- HBV DNA: 5.0×10^7 IU/ml
- ALT: 54
- HDV:neg

Mixed WT/Mut also found in 2623

MENITSGFLGPLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGG TTVCLGQNSQSPTSNHSPTSCPPTstopPGYRWMCLRRFIIFLF ILLLCLIFLLVLLDYQGMLPVCPLIPGSSTTSTGPCRTCTTPAQ GTSMYPSCCCTKPSDGNCTCIPIPSSWAFGKFLWEWASARF SWLSLLVPFVQWFVGLSPTVWLSVIWMMWYWGPSLYSILSP FLPLstopPIFFCLWVYI.