CHALLENGES IN THE ELIMINATION OF HEPATITIS VIRUSES:
THE ALASKA STORY AND BEYOND

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I personally have no conflict of interests for this talk.

The Liver Disease and Hepatitis Program at ANTHC receives research funding from 2 grants from Gilead Sciences. I am not listed as an investigator on these grants.
<table>
<thead>
<tr>
<th>Type</th>
<th>Genome</th>
<th>Route</th>
<th>Chronic/HCC</th>
<th>Vaccine</th>
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</thead>
<tbody>
<tr>
<td>Hepatitis A (HAV)</td>
<td>RNA</td>
<td>Fecal/Oral</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hepatitis B (HBV)</td>
<td>DNA</td>
<td>Parenteral</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Hepatitis C (HCV)</td>
<td>RNA</td>
<td>Parenteral</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Hepatitis D (HDV)</td>
<td>RNA</td>
<td>Parenteral (With HBV)</td>
<td>Yes</td>
<td>Yes/HBV</td>
</tr>
<tr>
<td>Hepatitis E (HEV)</td>
<td>RNA</td>
<td>Fecal/Oral</td>
<td>No</td>
<td>Yes</td>
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Hepatitis A Virus (HAV):
- Elimination of HAV transmission in Alaska
- Challenges in Global elimination of HAV

Hepatitis B Virus (HBV):
- The ANTHC HBV Program: Identification of persons with HBV, vaccination of susceptible persons and linkage to care for those found with chronic HBV infection
- Challenges in Global elimination of HBV

Hepatitis C Virus (HCV):
- HCV and Challenges to elimination in Alaska Native People
- Challenges in the Global elimination of HCV

Hepatitis D and E Viruses are not found in Alaska:
1. Recognizing viral hepatitis is a problem in Alaska that disproportionately has affected AN Peoples
2. Presenting this information to AN Tribal Boards and communities
3. Receiving support to conduct studies to Defining the epidemiology, transmission patterns and risk factors for liver related complications
4. Receiving Tribal approval to perform vaccine trials for hepatitis A and B
5. Designing programs with Tribal input and active participation to stop transmission of hepatitis A and B in Alaska
6. Receiving Tribal approval to study the epidemiology of hepatitis C prevalence, transmission and outcome
7. Designing programs with Tribal input and active participation to eliminate chronic hepatitis B and C
Prior to 1990, Alaska had the highest incidence of HAV infection in the US that disproportionately affected Alaska Native People (AN).

ANTHC and CDC Alaska (AIP) conducted the US childhood vaccine trial for licensure.

ANTHC and CDC conducted a study of HAV vaccine immunogenicity in infants and toddlers.

ANTHC, Alaska State Dept. of Health and four Tribal Health Corporations: South Central Foundation (SCF), Tanana Chiefs Conference (TCC), Maniilaq, North Sloop Borough and Norton Sound Health Corporation (NSHC) to stop a large epidemic of HAV prior to licensure by vaccinating 5,000 persons in 25 communities with one dose of (HAV) vaccine.

Working with the State of Alaska and Tribal Health Corporations to introduce universal hepatitis A vaccine for all children in Alaska regardless of ethnicity.
HEPATITIS A IN ALASKA NATIVES AND NON-NATIVES IN ALASKA, BY YEAR

- **Rate per 100,000**
- **Year**
- **Alaska Native**
- **Non-Native**
- **State of Alaska vaccination programs**

(CDC: Centers for Disease Control and Prevention)
Global Challenges for HAV

- In many countries with Indigenous Populations, HAV infection occurs in early childhood with little icteric/symptomatic disease.
- As sanitation improves in some countries, young children miss infection and outbreaks can occur in older susceptible persons.
- Hepatitis A vaccine could be used in these regions to:
  - Quickly stop outbreaks using large vaccination campaigns.
  - To prevent outbreaks with one or two doses of vaccine early in life.
- ANTHC and CDC together are conducting the longest trials to determine how long protection lasts.
  - Preliminary results show protection lasts for at least 22 years in those vaccinated earlier in life.
High Prevalence and Incidence rates were noted in AN Population in Western Alaska in the 1970’s along with high rates of hepatocellular carcinoma (HCC) even in children (due to HBV genotype F also found in Indigenous peoples in the Amazon).

Five genotypes of HBV were identified. Transmission was mother to infant in Northwest Alaska where genotype C predominated and person to person thru open cuts and scratches in children in SW Alaska where genotypes A, B, D and F were found.

In 1981, a vaccine trial with participation by Alaska Native Health Service, CDC AIP and DVH and two Alaska Native Tribal Health Corporations was conducted with halted transmission in 16 villages.

Immense political pressure by AN Tribal Groups was put on Alaska’s Congressional representatives to provide funding for a massive vaccination program.
ALASKA NATIVE HEPATITIS B PROGRAM

- Universal HBV Newborn vaccination introduced in 1983
- Screening and Catch-up vaccination of children and adults: 1983-1988
  - 53,000 persons screened; \( \frac{3}{4} \) of population, 90% in endemic areas of western Alaska
- No new cases of acute HBV in AN children since mid 1990’s
- No more AN children <20 have chronic HBV infection
- Rates of liver cancer in children which were the highest reported in world have fallen to zero since mid 1990’s
As of 2013, there are no Alaska Native children known to be HBsAg-positive.
HCC in Alaska Natives <20 years of age

P value for trend = 0.002

Hepatology 2011;54:801-7
GLOBAL BURDEN OF HBV

- **Prevalence**
  - 248 million persons with chronic HBV

- **Mortality:**
  - 15% to 40% with chronic HBV will die of liver cancer or liver failure if not under management
    - 25%-40% of males
    - 10-15% females
  - Average decrease in life span for a person not under care with chronic HBV is 6 years

- **Cirrhosis**
  - 10% to 20% of males and females

- **Currently about ~686,000 deaths worldwide per year**

Increase in liver-cancer deaths (past 20 years): Globally (from 1.25 to 1.75 million/year).
Global Prevalence of Chronic Hepatitis B

HBsAg prevalence

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<tbody>
<tr>
<td></td>
<td>&lt; 2%</td>
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<td>2-4.99%</td>
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<tr>
<td>5-7.99%</td>
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<td></td>
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<tr>
<td>≥8%</td>
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- Bering Sea Coastal Region 2-5%
- Arctic Canada 2-4%
- Indigenous peoples 4%
- Arctic Canada 5.6%
- Indigenous peoples 5.6%
CRUCIAL ACTIONS IN REDUCING MORBIDITY AND MORTALITY OF HBV GLOBALLY

- Newborn vaccination for HBV with selective catch-up vaccination
- Screening high risk persons and populations for HBV and linking those with chronic HBV to care.
  - CDC has determined the screening for HBV is cost effective in populations where the prevalence of HBsAg, the marker for active infection, is >2%
  - In US, this is all persons born in endemic countries and traditional high risk individuals
  - Globally, most countries have an HBsAg prevalence of >2% so this represents a challenge
Global Immunization 1989-2013, 3rd dose of Hepatitis B coverage in infants, global coverage at 81% in 2013

Immunization Vaccines and Biologicals, (IVB), World Health Organization.
194 WHO Member States. Date of slide: 29 July 2014.
NUMBER OF COUNTRIES HAVING INTRODUCED HEPATITIS B VACCINE AT BIRTH AND GLOBAL BIRTH DOSE COVERAGE, 2000-2013

Immunization Vaccines and Biologicals. (IVB), World Health Organization.
194 WHO Member States. Date of slide: 29 July 2014.

Myanmar is counted from 2004 to 2010 as the birth dose was removed from schedule in 2011.
Evidence of long-term protection from vaccination

- Studies from Alaska have found that evidence of humoral and cellular immunity in persons vaccinated >6 months of age last for at least 30 years
- For those vaccinated as newborns, duration of protection lasts at least 18 years
  - Duration only needed 1st 5 years of life to have greatest impact on reduction of chronic HBV
- Need for more serosurveys from MIC/LIC countries in children 5-years post infant vaccination

Bruce et al. J Infect Dis 2016;214:16-22
MATHEMATICAL MODEL: AGE-SPECIFIC HEPATITIS B-RELATED CIRRHOSIS AND HCC MORTALITY

Goldstein Int J Epidemiol 2005;34;1329-39
CHRONIC VIRAL HEPATITIS IN ALASKA NATIVE PEOPLE

- Chronic Hepatitis B
  - We currently care for 1181 patients with chronic HBV
    - >75% live in rural communities, mostly western Alaska
    - > 90% of these patients are linked to care
THE ANTHC HBV HEPATITIS REGISTRY

- Computerized registry containing pertinent clinical and laboratory data on all patients with chronic HBV/HCV
- Reminder letters are sent every 6 months to all patients
  - List of Patients in community/region sent to provider with lab slip with bar code
- Blood drawn in village clinic or hospital then centrifuged and separated
- Sera mailed ANMC lab for liver panel, AFP and HBV DNA
  - Results downloaded and reviewed by Hepatologist and HBV Registry RN who make evaluation and treatment decisions
- If all are normal, letter is sent back to patient with results
- If AFP > 10 ng/ml, patient is urged to go to nearest community for US
  - We found AFP has >95% negative predictive value for HCC but only 10% positive predictive value
  - Those with abnormal results are contacted by phone to arrange for radiographic studies if AFP > 10 mg/ml and those with abnormal liver function tests for further testing such as FibroScan and/or liver biopsy
### Linkage to Care for Alaska Native Persons with Chronic Hepatitis B

<table>
<thead>
<tr>
<th>Treatment Candidate</th>
<th>Linked</th>
<th>In clinic &lt; 12 months</th>
<th>Rx Candidate</th>
<th>On Rx</th>
<th>Treatment Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>^HBV DNA &gt; 20,000 IU/ml and ALT &gt; 2X ULN or HBV DNA &gt; 2,000 IU/ml, elevated ALT and liver biopsy with moderate to severe fibrosis (Ishak 3-6 or Knodell 3-4) or inflammation (HAI &gt;8) or receiving cancer chemo or immunosuppressive therapy</td>
<td>93.3%</td>
<td>63%</td>
<td>10.1%</td>
<td>81%</td>
<td>65%</td>
</tr>
</tbody>
</table>

Response = % ALT < 40, HBV DNA < 100 IU/ml

Unpublished data
GLOBAL ELIMINATION OF HBV

- **Birth dose and catch-up vaccination**
  - Vaccination of health care workers and at risks persons

- **Phased in screening for identification of those with chronic HBV Screening:**
  - Screening is currently taking place for blood product donors in many countries
  - Screening household contacts and persons with liver disease
  - Screening might be conjunction with HIV screening programs

- **Linkage to care and treatment**
  - Training of providers to manage HBV: Establishing centers of excellence
  - Laboratory capacity to do HBV DNA levels
  - Availability of antiviral medications
  - Screening to detect liver cancer (HCC) early when potentially curable
  - Capacity to treat early liver tumors
HOW WE LINK PERSONS WITH HCV TO CARE AND TREATMENT

- All persons in the ANTHC HCV Registry receive a letter every 6 months recommending they go to local Tribal Provider to have LFTs and AFP tested.
- Those with advanced fibrosis/cirrhosis (F3, F4) also receive a letter to get a liver US every 6 months.
- All persons are invited to visit liver clinic at ANMC or rural Hepatology clinics.
- We use Vidyo® clinics, telephone consultations and other means to help manage patient living in remote areas.
- Goal is to evaluate all persons with chronic HCV and treat those eligible.
Cascade of Care for Hepatitis C at ANTHC: >30,000 Persons Screened

- HCVAb+: 98%
- HCV RNA Tested: 62%
- HCV RNA +: 83%*
- Linked to care: 76%
- Treatment Candidates: 76%

*% of those linked to care who are HCV RNA+
Right now a “pipe dream” but actively pursued by the Hepatitis Alaska Working Group (HAWG)

Must consist of community wide participation to achieve any measure of success

Must include: Screening and Linkage to Care of:

- Baby Boomers and at risk adults: Considering expanding to all adults over 18
- Drug treatment programs, homeless persons, needle exchange programs
- Screening for hepatitis B and C in Prisons
  - Vaccination for those negative for HBV
  - Treatment for those positive for HCV
- Pregnant females: Started at Alaska Native Medical Center (ANMC) in Anchorage
- Emergency Departments
Hepatitis C Elimination Initiative

1) Identify

- Babyboomers
- Homeless
- Rural/Villages VTC
- Prisoners
- Emergency Department
- Enhanced Screening (Age 18+)
- Needle Exchange
- IDU on Treatment

LDHP – 2) Treat

Courtesy of Lisa Townshend
COLLABORATION WITH OTHER PARTNERS IN ALASKA

- All Alaska Native Tribal Health Organizations
- CDC; Arctic Investigations Program and Division of Viral Hepatitis
- State of Alaska Depts. of Epidemiology and Public Health Nursing
- Municipality of Anchorage
- University of Alaska, Anchorage
- University of Washington, Seattle
- WWAMI medical school program
- Private Sector
- The Hepatitis Alaska Working Group (HAWG)
  - Meets Quarterly to discuss collaboration on viral hepatitis
SCREENING AND LINKAGE TO CARE FOR HCV GLOBALLY

- Screening to identify those infected
  - Screening currently taking place for blood donors
  - Screening of persons for HCV with HIV and HBV
  - Coupling screening with HIV screening programs
  - Screening at needle exchange programs

- Linkage to Care and treatment
  - Training providers to treat HCV with DAA
  - Availability of testing for HCV RNA
  - Providing DAA at a reasonable cost