

HEPATITIS A VIRUS

- RNA Picornavirus
 - Single serotype worldwide
 - Acute disease and asymptomatic infection
- No chronic infection
 - Protective antibodies develop in response to infection - confers lifelong immunity



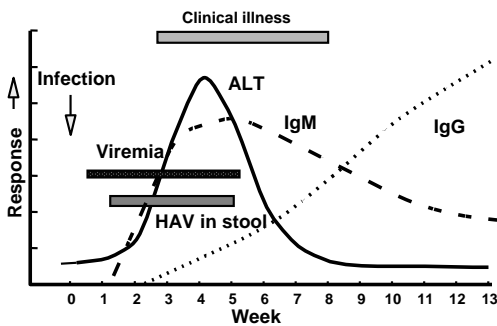
HEPATITIS A - CLINICAL FEATURES

- Jaundice by age group:

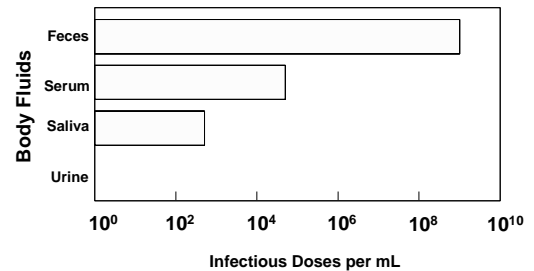
<6 yrs	<10%
6-14 yrs	40%-50%
>14 yrs	70%-80%
- Rare complications: Fulminant hepatitis
Cholestatic hepatitis
Relapsing hepatitis
- Incubation period: Average 30 days
Range 15-50 days
- Chronic sequelae: None



EVENTS IN HEPATITIS A VIRUS INFECTION



CONCENTRATION OF HEPATITIS A VIRUS IN VARIOUS BODY FLUIDS



Source: Viral Hepatitis and Liver Disease 1984:9-22
J Infect Dis 1989;160:887-890



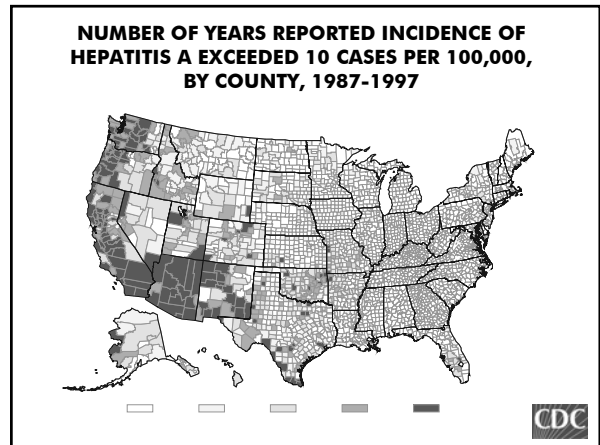
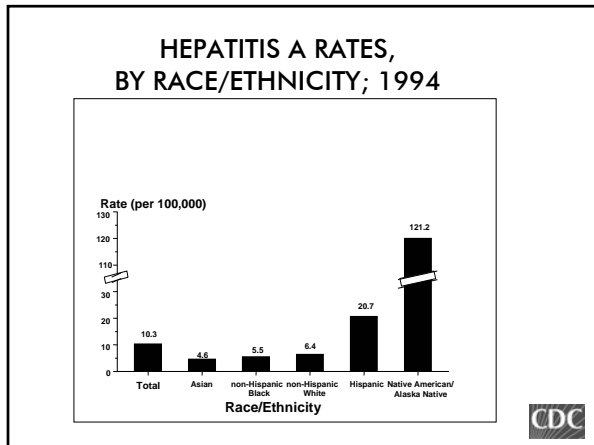
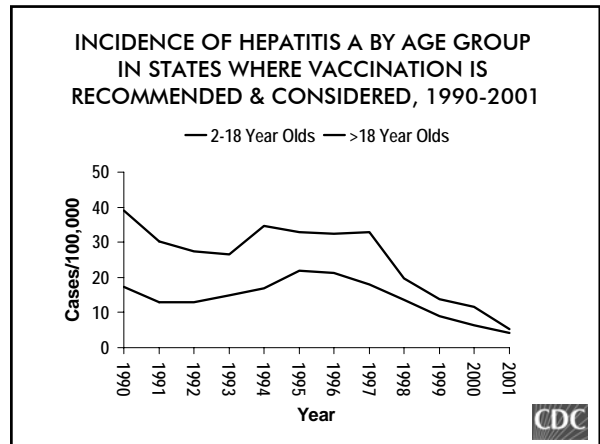
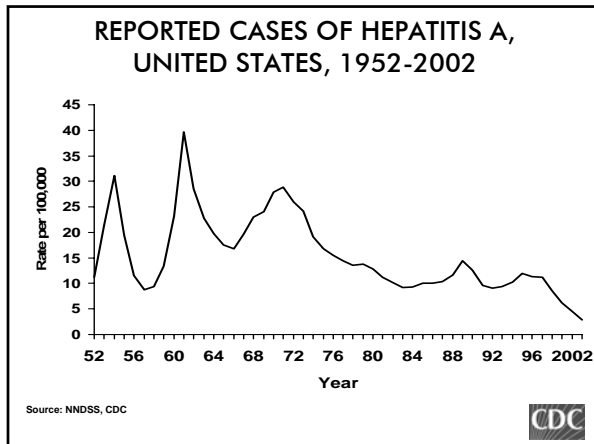
GEOGRAPHIC DISTRIBUTION OF HEPATITIS A VIRUS INFECTION



ACUTE HEPATITIS A CASE DEFINITION FOR SURVEILLANCE

- ◆ **Clinical criteria**
 - An acute illness with:
 - discrete onset of symptoms (e.g. fatigue, abdominal pain, loss of appetite, intermittent nausea, vomiting), **and**
 - jaundice or elevated serum aminotransferase levels
- ◆ **Laboratory criteria**
 - IgM antibody to hepatitis A virus (anti-HAV) positive
- ◆ **Case Classification**
 - Confirmed. A case that meets the clinical case definition and is laboratory confirmed or a case that meets the clinical case definition and occurs in a person who has an epidemiologic link with a person who has laboratory-confirmed hepatitis A (i.e., household or sexual contact with an infected person during the 15-50 days before the onset of symptoms).

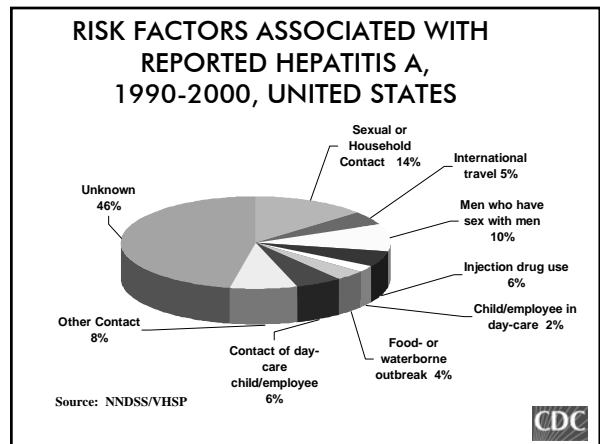




HEPATITIS A VIRUS TRANSMISSION

- Close personal contact (e.g., household contact, sex contact, child day-care centers)
- Contaminated food, water (e.g., infected food handlers)
- Blood exposure (rare) (e.g., injection drug use, rarely by transfusion)

Source: NNDSS, CDC



PREVENTING HEPATITIS A

- Hygiene (e.g., hand washing)
- Sanitation (e.g., clean water sources)
- Hepatitis A vaccine (pre-exposure)
- Immune globulin (pre- and post-exposure)



HEPATITIS A VACCINES

- Highly immunogenic
 - 97%-100% of children, adolescents, and adults have protective levels of antibody within 1 month of receiving first dose; essentially 100% have protective levels after second dose
- Highly efficacious
 - In published studies, 94%-100% of children protected against clinical hepatitis A after equivalent of one dose



HEPATITIS A VACCINES

Recommended Dosages of Hepatitis A Vaccines

Schedule Vaccine	Age (yrs)	Dose	Volume (mL)	2-Dose (mos)
HAVRIX®*	2-18	720 (EL.U.†)	0.5	0, 6-12
	>18	1,440	1.0	0, 6-12
VAQTA®**	2-18	25 (U**)	0.5	0, 6-18
	>18	50	1.0	0, 6-18

* EL.U. – Enzyme-linked immunosorbent assay (ELISA) units
 ** Units
 † has 2-phenoxylethanol as a preservative
 ‡ has no preservative



SAFETY OF HEPATITIS A VACCINE

- Most common side effects
 - Soreness/tenderness at injection site - 50%
 - Headache - 15%
 - Malaise - 7%
- No severe adverse reactions attributed to vaccine
- Safety in pregnancy not determined – risk likely low
- Contraindications - severe adverse reaction to previous dose or allergy to a vaccine component
- No special precautions for immunocompromised persons



DURATION OF PROTECTION AFTER HEPATITIS A VACCINATION

- Persistence of antibody
 - At least 5-8 years among adults and children
- Efficacy
 - No cases in vaccinated children at 5-6 years of follow-up
- Mathematical models of antibody decline suggest protective antibody levels persist for at least 20 years
- Other mechanisms, such as cellular memory, may contribute



COMBINED HEPATITIS A HEPATITIS B VACCINE

- Approved by the FDA in United States for persons ≥18 years old
- Contains 720 EL.U. hepatitis A antigen and 20 µg. HBsAg
- Vaccination schedule: 0,1,6 months
- Immunogenicity similar to single-antigen vaccines given separately
- Can be used in persons ≥ 18 years old who need vaccination against both hepatitis A and B
- Formulation for children available in many other countries



HEPATITIS A PREVENTION IMMUNE GLOBULIN

- Pre-exposure
 - ◆ travelers to intermediate and high HAV-endemic regions
- Post-exposure (within 14 days)
 - Routine
 - ◆ household and other intimate contacts
 - Selected situations
 - ◆ institutions (e.g., day-care centers)
 - ◆ common source exposure (e.g., food prepared by infected food handler)

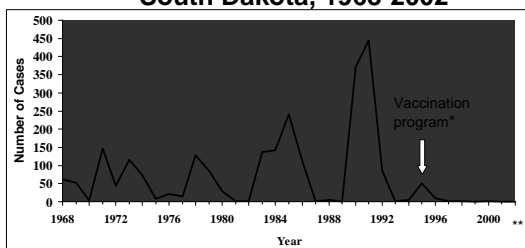


INCREMENTAL IMPLEMENTATION OF ROUTINE HEPATITIS A VACCINATION OF CHILDREN

- 1996 - Children living in communities with the highest rates
- 1999- Children living in states/communities with consistently elevated rates during "baseline period"
- All children nationwide



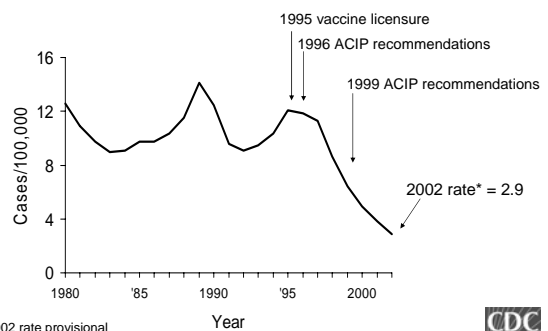
Reported Hepatitis A Cases, By Year Northern Plains Indian Reservation† South Dakota, 1968-2002



* Estimated first dose coverage (children 2-12 years) = 71%
 ** 2002 Preliminary data
 † Counties: Bennett, Corson, Dewey, Jackson, Roberts, Shannon, Todd, Ziebach
 * † Source: South Dakota Department of Health



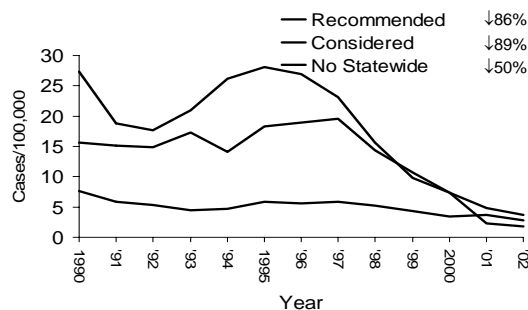
Hepatitis A Incidence, United States, 1980-2002*



*2002 rate provisional



Incidence of Hepatitis A by U.S. Region, 1990-2002*



*2002 rate provisional



TOP 10 STATES WITH THE HIGHEST HEPATITIS A RATES

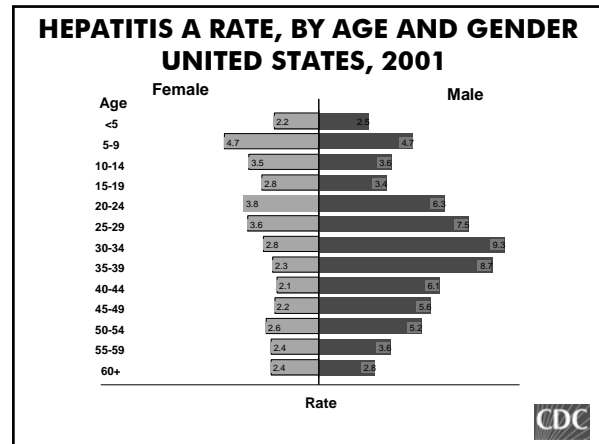
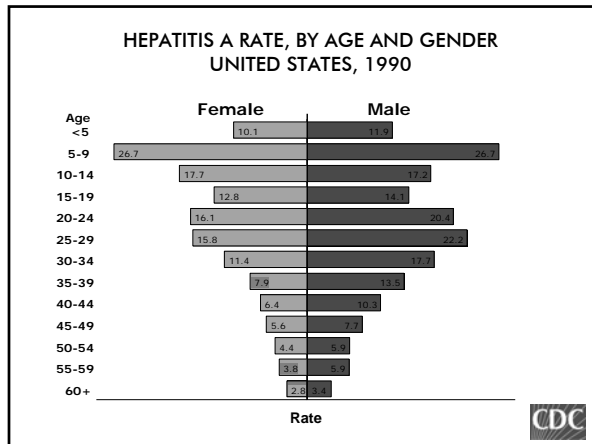


THEN
1987-1997

	Avg. rate		Rate
Arizona	48	D.C.	14
Alaska	45	Georgia	12
Oregon	40	Arizona	8
New Mexico	40	Rhode Island	7
Utah	33	Connecticut	7
Washington	30	Kansas	7
Oklahoma	24	Maryland	6
South Dakota	24	Massachusetts	6
Idaho	21	Texas	6
Nevada	21	Florida	5
California	20	California	5

NOW
2001





- ### ACIP RECOMMENDATIONS PERSONS AT INCREASED RISK OF INFECTION, 1996
- Men who have sex with men
 - Illegal drug users
 - International travelers
 - Persons who have clotting factor disorders
 - Persons with chronic liver disease
-

STD Treatment Guidelines MMWR May 10, 2002 51(RR06)

“Vaccination against hepatitis is the most effective means of preventing sexual transmission of hepatitis A and B.”

- ### HEPATITIS A IN THE UNITED STATES -2002
- National rate lowest yet recorded
 - ◆ Continued monitoring needed to determine if low rates sustained and due to vaccination
 - ◆ Evaluation of age-specific rates to assess impact of vaccination strategy
 - Rates increasing in some states
 - ◆ Occurring among adults in high risk groups (e.g. MSM, drug users)
-

- ### HEPATITIS A VACCINATION IN THE UNITED STATES CHALLENGES FOR THE FUTURE
- Continue implementation of the current recommendations for vaccination of children
 - ◆ Sustain vaccination in face of falling rates
 - Further reduce incidence
 - ◆ Vaccination of high-risk adults
 - ◆ Vaccination of children nationwide
-

Hepatitis B : A Clinical Perspective

Adapted by Jill Gallin, CPNP
Assistant Professor of Clinical Nursing

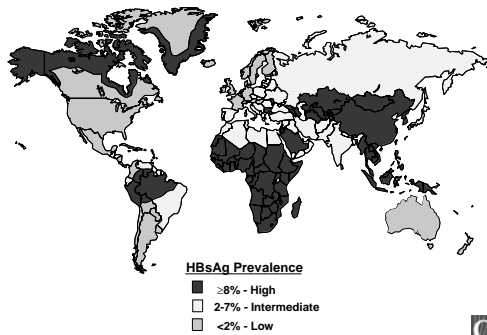


Hepatitis B Overview

- Serious: Causes death from liver disease in up to 25% of those infected at birth.
- Cancer related: Liver cancer especially prevalent in areas of world where hepatitis B is common.
- Disease of refugees: New arrival Southeast Asian refugees (1 out of 2 is immune, 1 out of 7 is a carrier, 1 out of 3 is susceptible).
- Preventable: Safe, effective, and affordable vaccination is available.



Geographic Distribution of Chronic HBV Infection

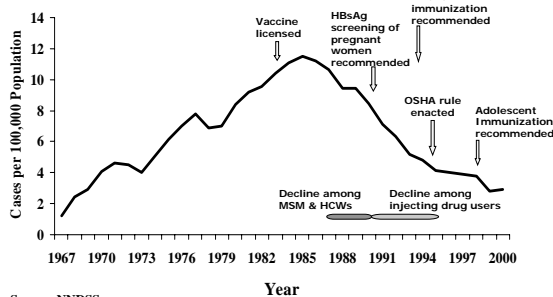


Hepatitis B Incidence in U.S., 2001

- Estimated incidence
 - ◆ 78,000 cases/year
- Reported cases
 - ◆ Acute hepatitis B: 7,844



Hepatitis B by Year, United States, 1966 - 2000



Transmission of HBV (1)

- Concentration of HBV in various body fluids
 - ◆ **High:** Blood, serum, wound exudates
 - ◆ **Medium:** saliva, semen, and vaginal secretions
 - ◆ **Low/not detectable:** urine, feces, sweat, tears, breastmilk
- Perinatal – transplacental transmission, rare (2-5%)
- Sexual transmission – unprotected sex



Transmission of HBV (2)

- Percutaneous transmission – sharing of injection drug use equipment, needle stick injury, ear-piercing, body piercing, tattooing, inadequate sterilization of medical equipment, scarification
- Household and interhousehold transmission – less risk but significant - can occur in settings such as shared toothbrushes, razors, combs, washcloths



Transmission of HBV (3)

- Passed from child to child by biting, shared objects, oozing cuts, impetigo, etc.
- Virus can exist on environmental surfaces for up to one week and remain infectious.
- Pre-chewing food for babies, or sharing food that has been chewed by someone else (chewing gum).



Transmission of HBV (4)

- Institutionalized settings – risks of biting, sexual abuse
- More than 1/4 of acute cases have no readily identifiable risk factor
- Not spread by sneezing or coughing, sharing eating utensils.



Risk Groups for HBV Infection (1)

- Immigrants/refugees from areas of high HBV endemicity (Asia, Pacific Islands, Sub-Saharan Africa, Amazon Basin, E. Europe, Middle East)
- Children born in U.S. to immigrants from areas of high HBV endemicity
- Alaska Natives and Pacific Islanders
- Household contacts and sex partners of people with chronic HBV infection



Risk Groups for HBV Infection (2)

- People who have or who have had sexually transmitted diseases
- Heterosexuals with >1 sex partner in 6 months
- Men who have sex with men
- Users of illicit injectable drugs
- Health care workers in contact with blood



Risk Groups for HBV Infection (3)

- Adopted children from mod/high-risk countries
- Hemodialysis patients
- Recipients of certain blood products
- Clients/staff at institutions for the developmentally disabled
- Inmates of long-term correctional facilities



Hepatitis B Nomenclature and/or Lab Tests (1)

- **HBV:** Hepatitis B virus.
- **HBsAg:** Hepatitis B surface antigen. Marker of infectivity when found in serum.
- **anti-HBs:** Antibody to HBsAg. Marker of immunity when found in serum.
- **HBcAg:** Hepatitis B core antigen. No commercial test available for this.
- **anti-HBc:** Antibody HBcAg. Marker of past or current infection.



Hepatitis B Nomenclature and/or Lab Tests (2)

- **IgM anti-HBc:** IgM is an antibody subclass of anti-HBc. Indicates recent infection with HBV (<4-6 mos.).
- **IgG anti-HBc:** IgG is a subclass of anti-HBc. Indicates "older" infection with HBV.
- **HBeAg:** Hepatitis B "e" antigen. Can only be present if HBsAg is positive. Marker of high degree of infectivity.
- **Anti-HBe:** Antibody to "e" antigen. May be present in infected or immune person.



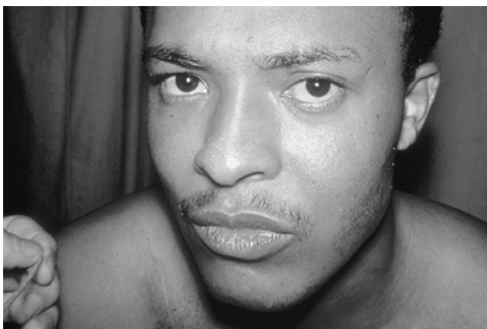
Hepatitis B Nomenclature and/or Lab Tests (3)

- **HBIG:** Hepatitis B immune globulin. Passively delivered antibody that provides "instant" protection against HBV.
- **HCC/PHC:** Hepatocellular carcinoma, primary hepatocellular carcinoma.
- **HDV:** Hepatitis D virus (the delta virus). Etiologic agent of delta hepatitis. Can cause infection only in the presence of HBV infection.



Hepatitis B: Clinical Features

- Incubation period ranges from 45-180 days, average is 60-90 days
- Onset is insidious
- Clinical illness (jaundice): <10% for <5 yr olds
30%-50% for >5 yrs
- Acute case-fatality rate: 0.5%-1%
- Chronic infection: <5 yrs old, 30%-90%
>5 yrs old, 2%-6%
- Premature mortality from chronic liver disease: 15%-25%



Acute Viral Hepatitis

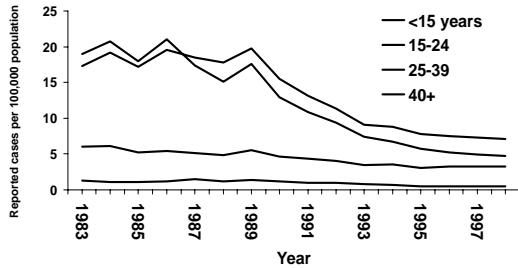


Signs and Symptoms

- Symptom
 - ◆ there may be none
 - ◆ loss of appetite, malaise, nausea, vomiting, abdominal pain, arthralgias, myalgias
- Signs
 - ◆ there may be none
 - ◆ jaundice, fever, dark urine



Reported Cases of Hepatitis B, by Age, U.S., 1983-1998



Source: NNDS



Interpretation of Hepatitis B Panel

HBsAg antiHBc antiHBs	negative negative negative	susceptible
HBsAg antiHBc antiHBs	negative positive positive	immune due to natural infection
HBsAg antiHBc antiHBs	negative negative positive	immune due to vaccine
HBsAg antiHBc IgM antiHBc antiHBs	positive positive positive negative	acutely infected
HBsAg antiHBc IgM antiHBc antiHBs	positive positive negative negative	chronically infected
HBsAg antiHBc antiHBs	negative positive negative	four possible interpretations (see next slide)



Natural History

- Likelihood of becoming a carrier varies inversely with the age at which infection occurs.
- Pool of carriers in U.S. is 1-1.25 million persons.
- ~5000 persons die/yr. from HBV-related cirrhosis.



Risk of Becoming Chronically Infected with HBV

- 2% - 6% of older children and adults
- 20% - 50% of children <5 yrs
- 85% - 90% of infants infected at birth



Treatment for HBV

- Three FDA-licensed treatment options available for adults in the United States
 - ◆ interferon alfa-2b (IntronA), recombinant administered subcutaneously qd or 3x/wk
 - * also licensed for use in children
 - ◆ lamivudine (Epivir-HB) administered by mouth qd
 - ◆ adefovir dipivoxil (Hepsera) administered by mouth qd

Consult a liver specialist to assist in determining whether your patient is a treatment candidate.



Monitoring HBsAg+ Patients

- Discuss monitoring with a liver specialist having much experience in managing viral liver diseases.
 - ◆ Annual physical exam.
 - ◆ Blood work every 6-12 mos.
 - ◆ Liver biopsy?
 - ◆ Liver ultrasound or CT scan every 6-12 mos.
 - ◆ "fetoprotein (AFP) every 6-12 mos.
- Education of patient about disease.



Management of Family Members of HBsAg+ Patients

- Test all family members with hepatitis B panel (HBsAg, antiHBc, antiHBs)
- For those susceptible, vaccinate
- For susceptible sex partner(s), test after 3 doses to be sure s/he converts to antiHBs+
- Education of family members



This Khmer woman died of hepatoma, four months after arriving in a refugee camp in Thailand.

Source: Patricia Walker, MD



Hepatocellular Carcinoma – HCC (1)

- HBV leads to liver cancer
 - ◆ epidemiologic correlation in many populations
 - ◆ risk for HCC is 12-300 times greater in HBsAg+ persons
 - ◆ HBV DNA is incorporated into DNA of hepatoma cells
- Incidence
 - ◆ peak incidence is in 40-60 yr olds
 - ◆ in Taiwan, #1 cause of death for men >40 yrs
 - ◆ 0.25-1 million deaths/year in the world
 - ◆ over 1500 persons die/yr in the U.S. from HCC
 - ◆ HCC is 3-4x more common in HBsAg+ men than women



Hepatitis B Prevention (1)

- Hepatitis B Immune Globulin (HBIG)
 - ◆ provides temporary passive protection
 - ◆ indicated in certain postexposure settings
- Hepatitis B Vaccine
 - ◆ vaccinate all children 0-18 years of age
 - * infant schedule: **birth dose preferred** (0, 1-2, 6), (0, 1-4, 6-18)
 - Schedule if using monovalent vaccine followed by Comvax®: (0, 2, 4, 12)
 - * children/teens: (0, 1, 6), (0, 1-2, 4), (0, 1, 6-12) or (0, 12, 24) month schedule. There is also a two-dose schedule for 11-15 year olds using Recombivax HB® only. This schedule is 0, 4-6 months.



Hepatitis B Prevention (2)

- Hepatitis B Vaccine (continued)
 - ◆ Vaccinate all high-risk individuals
 - * Adult schedule (0, 1-2, 6)
 - * Testing can be done if concern that patient has been previously infected, but do not delay administering first dose of vaccine until a later visit; test, then give first dose.
- Hepatitis B Prenatal Testing
 - ◆ Test **EVERY** pregnant woman during every pregnancy for HBsAg, even if she has been immunized against hepatitis B or is chronically infected.
 - ◆ Send a copy of the original lab report to the hospital.



Childhood or Adult Schedule



Never start the series over!
Never! Never!
Never!

Recommended dosages of hepatitis B vaccines *

Vaccine brand	Age group	Dose	Volume	# Doses
Engerix-B (GSK)	0-19 years	10 µg	0.5 ml	3
	20 years and older	20 µg	1.0ml	3
Recombivax HB (Merck & Co.)	0-19 years	5 µg	0.5 ml	3
	11-15 years	10 µg	1.0 ml	2
	20 years and older	10 µg	1.0 ml	3

* The schedule for hepatitis B vaccination is flexible and varies. Consult the ACIP statement on Hepatitis B (11/91), AAP's 2000 Red Book, or the package insert for details.

Note! For adult dialysis patients: the Engerix-B dose required is 40µg/2.0ml (use the adult 20µg/ml formulation) on a schedule of 0, 1, 2, and 6 months. For Recombivax HB, a special formulation for dialysis patients is available. The dose is 40µg/1.0ml and it is given on a schedule of 0, 1, and 6 months.

Prevention Schedule for Infants of HBsAg-POSITIVE Mothers

- HBIG 0.5 ml IM within 12 hrs. of birth.
- Dose #1 of Hep B vaccine in the opposite thigh within 12 hrs. of birth.
- Dose #2 of Hep B vaccine at 1-2 mos.
- Dose #3 of Hepatitis B vaccine at 6 mos.
- Testing for antiHBs and HBsAg 9-15 mos.
 - ◆ If negative for both, repeat the series and test 1-2 months later!



Schedule for infants of mothers with UNKNOWN HBsAg status

- Test mother for HBsAg in hospital ASAP.
- If mother's test is positive, give HBIG ASAP (within 7 days of birth).
- Give dose #1 of Hep B vaccine within 12 hrs. of birth. DO NOT DELAY THIS DOSE waiting for the lab result.
- Dose #2 of Hep B vaccine at 1-2 mos.
- Dose #3, follow dosing schedule based on mother's HBsAg status.



Schedule for infants with HBsAg-NEGATIVE mothers

- Dose #1 recommended to be given at birth.
- Dose #2 can be given at 1-4 mos. of age
- Dose #3 at 6-18 mos. of age
 - ◆ Final dose should NOT be given before age 6 mos.
 - ◆ May also give monovalent hepatitis B #1 at birth followed by 3 doses of Comvax[®] at 2, 4, and 12-15 mos., or 3 doses of Pediarix[®] at 2, 4, and 6 mos.



Dosing schedule for older children and teens (NOT INFANTS)

- **Rule #1:** There must be at least 4 wks. between dose #1 and dose #2.
- **Rule #2:** There must be at least 8 wks. between dose #2 and dose #3.
- **Rule #3:** There must be at least 4 mos. between dose #1 and dose #3.
- **Rule #4:** No matter how delayed dose #2 or #3 is, do not start the series over again.
- **Suggested spacing options:** 0, 1-2, 4-6 mos.; 0, 2, 12 mos.; 0, 12, 24 mos.



Dosing Schedule for Adults

- 0, 1, 6 month interval is standard for HCWs
 - ◆ Space dose #1 and #2 four wks. apart
 - ◆ Space dose #2 and #3 five mos. apart
- Alternative schedules 0, 2, 4; 0, 1, 4
- Never re-start the series if dosing was delayed. Continue from where you left off.
- Use a 1" or 1.5" needle. If obese, use 2".
- Injection must be intramuscular in deltoid.



Recommended post-exposure prophylaxis or exposure to HBV

Vaccination and antibody response status of exposed workers	Treatment		
	Source HBsAg positive	Source HBsAg negative	Source unknown or not available for testing
Unvaccinated	HBIG x 1 and initiate HB vaccine series	Initiate HB vaccine series	Initiate HB vaccine series
Previously vaccinated			
Known responder	No treatment	No treatment	No treatment
Known non-responder*	HBIG X 1 and initiate revaccination or HBIG X 2	No treatment	If known high risk source, treat as if source were HBsAg positive
Antibody response unknown	Test exposed person for anti-HBs 1. If adequate, no treatment is necessary. 2. If inadequate*, administer HBIG x 1 and vaccine booster.	No treatment	Test exposed person for anti-HBs 1. If adequate, no treatment is necessary. 2. If inadequate*, administer vaccine booster and recheck titer in 1-2 months.

* A non-responder is a person with inadequate levels of serum antibody to HBsAg (i.e., anti-HBs <10 mIU/mL)
Source: MMWR, June 29 2001, vol 50, RR-11, p22



Elimination of Hepatitis B Virus Transmission: United States

Objectives

- Prevent chronic HBV infection
- Prevent chronic liver disease
- Prevent primary hepatocellular carcinoma
- Prevent acute symptomatic HBV infection



Elimination of Hepatitis B Virus Transmission: United States

Strategy

- Prevent perinatal HBV transmission
- Routine vaccination of all infants
- Vaccination of children in high-risk groups
- Vaccination of adolescents
 - all unvaccinated children at 11-12 years of age
 - "high-risk" adolescents at all ages
- Vaccination of adults in high-risk groups



AAP, AAFP, and ACIP Recommend Hepatitis B "Catch-up"

- Give hepatitis B vaccine to all children 0-18 y.o.
- "Providers should make special efforts" to catch-up children (of parents) from moderate/high risk endemic areas.

References: Harmonized Childhood Immunization Schedule

CDC. Recommended childhood immunization schedule- U.S., Jan-Dec 1998 *MMWR* 1998; 47:10-1

CDC. Recommended childhood immunization schedule- U.S., Jan-Dec 1998 *MMWR* 1999; 48:14-5

CDC. Recommended childhood immunization schedule- U.S., Jan-Dec 1998 *MMWR* 2000; 49:36-7



Remember...

You should never start the hepatitis B vaccine series over again, no matter how long each dose is delayed!



References

Deborah L. Wexler, MD
Executive Director
Immunization Action Coalition
www.immunize.org

