Approved: 2-11-99
Date

MINUTES OF THE SENATE COMMITTEE ON PUBLIC HEALTH AND WELFARE.

The meeting was called to order by Chairperson Sandy Praeger at 10:00 a.m. on February 2, 1999 in Room 526-S of the Capitol.

All members were present except:

Committee staff present: Emalene Correll, Legislative Research Department
Norman Furse, Revisor of Statutes
JoAnn Bunten, Committee Secretary

Conferees appearing before the committee:

Sally Finney, Executive Director, Kansas Public Health Association, Inc.
Francisco Averhoff, M.D., Centers for Disease Control and Prevention
Carol Cowden, Immediate Pat Director, Mid American Immunization Coalition

Others attending: See attached list

**Presentation on Hepatitis B**

Sally Finney, Executive Director, Kansas Public Health Association, Inc., gave a background briefing on the current status of Hepatitis B immunization in Kansas. The Kansas Public Health Association is collaborating with other organizations in the state to help bring Kansas into compliance with a recommendation by the Centers for Disease Control and Prevention that all 11-year olds be immunized against Hepatitis B virus. This year Kansas began requiring immunization against Hepatitis B for entry into kindergarten. Ms. Finney noted that the Kansas Department of Health and Environment has agreed to recommend Hepatitis B immunization for entry into middle school (grade 6) beginning with the 1999-2000 school year, then require it for the following year, assuming funds are available to do so. Kansas Medicaid, HealthWave, and some private insurers already cover the cost of this immunization, however, additional funds will be needed to help vaccinate children who lack coverage for this service. Information from KDHE shows the cost of this effort can be more than adequately covered by earmarking $250,000 in the existing immunization program, and adding to that source no more than $100,000 from the Governor's budget request. The Governor's FY 2000 budget recommendations include $250,000 of additional state dollars for immunizations from the state's portion of the settlement in the lawsuit against the nation's four major tobacco companies. (Attachment 1) During Committee discussion on vaccination requirements for children entering the public school system, it was questioned what vaccination requirements effect home schoolers.

Francisco Averhoff, M.D., medical epidemiologist with the National Immunization Program, Centers for Disease Control and Prevention provided testimony on Hepatitis B that addressed clinical aspects of the disease, the epidemiology of Hepatitis B virus, the effectiveness and safety of Hepatitis B vaccine and a report on the experience with vaccinating adolescents with this vaccine nationally. To supplement his testimony, Dr. Averhoff provided copies of slides and a Question and Answer sheet about Hepatitis B vaccine developed at the CDC. (Attachment 2) During Committee discussion, Dr. Averhoff noted that nineteen states have adopted the Hepatitis B Vaccine Middle School Entry Requirements, and Florida was the first state to adopt such a requirement. He also pointed out that 30,000 children are infected annually by Hepatitis B in the U.S. and treatment for this disease is not very effective. The mode of transmission of Hepatitis B is very similar to the AIDS virus, and children who live in a household of a person with Hepatitis B have a high risk of being infected with the disease.

Carol Cowden, Past Director of Mid America Immunization Coalition, briefed the Committee on the Kansas City metropolitan middle school-based immunization program which began three years ago as a small pilot project in two Kansas City middle schools. Ms. Cowden noted that they started out with seed money from Merck Vaccine Division as well as funding help from area managed care companies, foundations and other private funders. Last March, the state of Missouri provided funding so that all Missouri children from infancy through age 18 could receive the shots at no cost, thereby covering the vaccine cost of immunization of all

Kansas City, Missouri children in the program. (Attachment 3) Committee discussion related to funding of the Hepatitis B vaccination program in Kansas, who could be exempt from the vaccination if on religious or medical grounds, and whether legislation would be required to carry out the Hepatitis B vaccination program or if it could be done by rules and regulations.

Written testimony in support of the vaccination program was received from the Kansas State Nurses Association. (Attachment 4)

**Adjournment**

The meeting was adjourned at 11:00 a.m.

The next meeting is scheduled for February 3, 1999.

# SENATE PUBLIC HEALTH AND WELFARE COMMITTEE
# GUEST LIST

DATE: 2-2-99

| NAME | REPRESENTING |
|---|---|
| Carolyn Maddendorf | KSNA |
| Jim Wood | Via Christi Health System |
| Rick Guthrie | Health Midwest |
| Kathy Damron | St. Luke Shawnee Mission |
| Danielle Noe | Governors Office |
| Stacy Soldan | Hein + Wilson Assoc |
| Bill Sneed | Merck |
| Bob Williams | Ks. Pharmacists Assoc |
| Barbara Belcher | Merck |
| Larrie Ann Brown | KS Assoc of Health Plans |
| Jean A Neal Jr | SmithKline Beecham |
| Donna Miller | Mid America Immunization Coalition |
| KEITH R LANDIS | CHRISTIAN SCIENCE COMMITTEE ON PUBLICATION FOR KANSAS |
| Lawrence Penny | Kansas Department of Corrections |
| Sally Finney | Ks. Public Health Assoc. |
| Cassie Cowden | Mid Am. Imm. Coalition |
| ORION BELL | American Red Cross |
| FRANCISCO AUENHOFF | Centers for Disease Control |
| Mary Kapp | Washburn University |

SENATE PUBLIC HEALTH AND WELFARE COMMITTEE
GUEST LIST

DATE: 2-2-99

| NAME | REPRESENTING |
|---|---|
| Deb Roberts | Kansas State Nurses Assn. |
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KANSAS PUBLIC HEALTH ASSOCIATION, INC.

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Testimony on Hepatitis B Disease
Presented on February 2, 1999
by Sally Finney, M.Ed, Executive Director

Thank you, Senator Praeger, and members of the committee for inviting us to appear before you today to discuss Hepatitis B disease as a public health threat. There are three of us here to present various aspects of Hepatitis B. Dr. Francisco Averhoff, who is here with us today from the Centers for Disease Control and Prevention in Atlanta, will give a basic overview of Hepatitis B disease and CDC's recommendations regarding it. Carol Cowden, former director of the Mid America Immunization Coalition will end with her experiences in the Kansas City, Kansas area. I will open by giving you some background on the current status of Hepatitis B immunization in Kansas.

The Kansas Public Health Association is collaborating with other organizations in the state to help bring Kansas into compliance with a recommendation by the Centers for Disease Control and Prevention that all 11-year-olds be immunized against Hepatitis B virus. This year, Kansas began requiring immunization against Hepatitis B for entry into kindergarten. By focusing on middle school students for a five-year period, today's kindergarten students, already immunized against the virus, will be entering middle school the Kansas will be in compliance with CDC's recommendation.

Because Hepatitis B prevention impacts a broad number of public health areas, including cancer prevention and safety of the organ/blood donor pool, we have been able to garner broad support for this request. Our coalition includes the Kansas Public Health Association, Kansas State Nurses Association, Mid America Immunization Coalition, the Kansas Medical Society, the American Cancer Society, the American Red Cross, and the Midwest Organ and Tissue Bank.

The Kansas Department of Health and Environment has agreed to recommend Hepatitis B immunization for entry into middle school (grade 6) beginning with the 1999-2000 school year then require it for the following year, assuming funds are available to do so. Kansas Medicaid, Health Wave, and some private insurers already cover the cost of this immunization. Additional funds will be needed to help vaccinate children who lack coverage for this service. Project the exact cost of this effort is impossible because some middle school students will already be immunized. Information provided to our coalition by KDHE shows the cost of this effort can be more than adequately covered by earmarking $250,000 in the existing immunization program and adding to that source no more than $100,000 from the Governor's budget request. The Governor's SFY 2000 budget recommendations include $250,000 of additional state dollars for immunizations from the state's portion of the settlement in the lawsuit against the nation's four major tobacco companies.

I will be glad to answer any questions you have at this time.

Senate Public Health and Welfare
Date: 2-2-99
Attachment No. 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention

February 1, 1999

My name is Francisco Averhoff, M.D.,M.P.H. and I am a medical epidemiologist with the National Immunization Program, Centers for Disease Control and Prevention (CDC). I will provide testimony on hepatitis B. Specifically, I will address clinical aspects of the disease, the epidemiology of hepatitis B virus, the effectiveness and safety of hepatitis B vaccine and report on the experience with vaccinating adolescents with this vaccine nationally.

To supplement my testimony, I have attached copies of slides and a Question and Answer (Q & A) sheet about hepatitis B vaccine developed at the CDC. Thank you for this opportunity to discuss this serious infectious disease and how to prevent it with vaccination.

Sincerely,

Francisco Averhoff

Senate Public Health and Welfare
Date: 2-2-99
Attachment No. 2

# Adolescent Immunization with Hepatitis B Vaccine

## Hepatitis B, Clinical Aspects

| | |
|---|---|
| Definition | Inflammation of the liver |
| Etiology | Hepatitis B virus |
| Transmission | Sexual, parenteral, perinatal, household, other |
| Infectivity | High: 100 times more than HIV |

## Estimates of Acute and Chronic Disease Burden for Hepatitis B, United States, 1997

| | |
|---|---|
| Acute Infections | 200,000 |
| Hospitalzed | 11,000 |
| Chronic Infections | 1.25 million |
| Deaths | 4,000 - 5,000 |

Source: CDC unpublished data

## Effect of Missed Opportunity to Vaccinate An Adolescent Cohort Against Hepatitis B Virus (HBV)

- 160,000 HBV infections
- 10,000 chronic HBV infections
- 1,400 deaths

Cohort size: 4.0 million
Source : Ambulatory Pediatric Association, 1998, N Smith et al

## Hepatitis B Vaccine

- Recombinant
- 3 dose series
- Highly immunogenic (>90% respond)
- Highly Efficacious (protects for at least 15 years)

## Vaccine Safety I

- Methods
  - Pre-licensure
  - Post-licensure
    - Vaccine Adverse Events Reporting System
    - Vaccine Safety Datalink
    - Case Reports
    - Institute of Medicine

## Vaccine Safety II

- Pre-licensure
  - >200,000 w/o serious adverse events
  - not designed to detect rare events
- Post-licensure
  - >500 million persons
  - various rare events reported

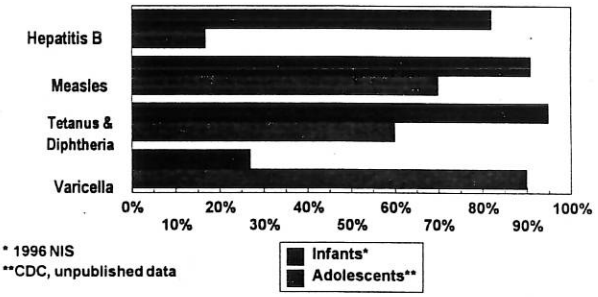
## Vaccine Safety III

- ***Associated***
  - anaphylaxis; 1/600,000, no deaths
- ***Case Reports; no evidence of association.***
  - Guillain-Barre Syndrome, transverse myelitis, optic neuritis, seizure, multiple sclerosis, other demyelinating diseases, alopecia, sudden infant death syndrome

## Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP)

- **All children and adolescents 0-18 years of age**
- **All high risk adults**

## Vaccination Coverage and Immunity Estimates of Adolescents and Infants, United States, 1996




* 1996 NIS
**CDC, unpublished data

## Adolescent Immunization Goals*, 1997

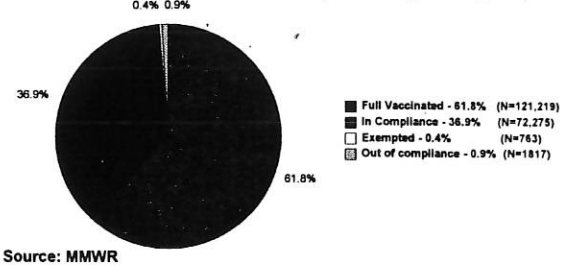
***For adolescents age 13 yrs. or in 8th grade:***

| | Year 2000 | Year 2002 |
|---|---|---|
| Hepatitis B-3 | 65% | 90% |
| MMR-2 | 90% | 90% |
| Td | 65% | 90% |
| Varicella, if susceptible | 65% | 90% |
| All (3:2:1:1) | 65% | 90% |

* Proposed for adoption, CDC partners meeting, Atlanta, 1997

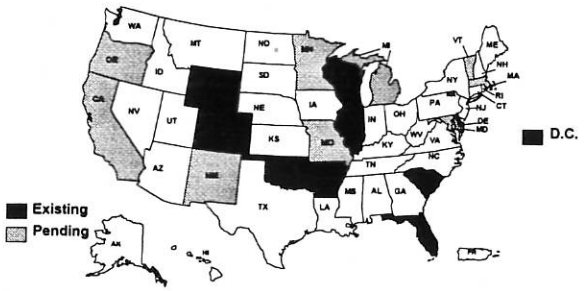
## Vaccination Coverage Among Florida Seventh Grade, October, 1997

**Florida Seventh Grade Population (N=196,074)**




Source: MMWR

## States with Hepatitis B Vaccine Middle School Entry Requirements, 1998




Source: Immunization Action Coalition Survey, 1998

-19 states

# Questions and Answers about Hepatitis B and the Vaccine that Protects You

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References

## Questions and Answers about hepatitis B and and The Vaccine That Protects You

### Q. **What is hepatitis B?**

A. Hepatitis B is a serious disease caused by the hepatitis B virus (HBV) which is present in the blood and body fluids of an infected individual. The virus can be transmitted from mother to baby at birth as well as through unprotected sexual intercourse, and unsterilized needles. Transmission is also possible with household contacts and from child to child. HBV infection can cause acute illness that leads to loss of appetite; tiredness; pain in muscles, joints, or stomach; diarrhea or vomiting; and yellow skin or eyes (jaundice). HBV can also cause chronic infection, especially in infants and children, that leads to liver damage (cirrhosis), liver cancer, and death. Each year in the United States, an estimated 200,000 people have new HBV infections, of whom more than 11,000 people are hospitalized and 20,000 remain chronically infected. Overall, an estimated 1.25 million people in the United States have chronic HBV infection, and 4,000 to 5,000 people die each year from hepatitis B related chronic liver disease or liver cancer *(Centers for Disease Control and Prevention (CDC), 1990; Margolis, 1991; West, 1992).*

Q. **How is hepatitis B vaccine used to prevent hepatitis B and its related complications?**

A. Hepatitis B vaccine prevents both HBV infection and those diseases related to HBV infection. It has been available since 1982. Hepatitis B vaccines currently available in the United States are made using recombinant DNA technology, and contain only a portion of the outer protein of HBV or hepatitis B surface antigen [HBsAg] *(Emini, 1986; Stephenne, 1990)*. The vaccine does not contain any live components. The vaccine is given as a series of three intramuscular doses. More than 95 percent of children and adolescents, and more than 90 percent of young, healthy adults develop adequate antibody to the recommended series of three doses *(Szmuness, 1980; Zajac, 1986; Andre, 1989)*. Persons who respond to hepatitis B vaccine are protected against acute hepatitis B as well as the chronic consequences of HBV infection, including cirrhosis and liver cancer *(CDC, 1991 a; Hadler, 1992)*.

Q. **For whom is hepatitis B vaccine recommended?**

A. The Advisory Committee on Immunization Practices (ACIP) recommends hepatitis B vaccine for everyone 18 years of age and younger, and for adults over 18 years of age who are at risk for HBV infection *(CDC, 1991 a,b; CDC, 1996; CDC, 1997; ACIP, 1998; Humiston, 1998)*. Hepatitis B vaccine has been recommended as a routine infant vaccination since 1991, and as a routine adolescent vaccination since 1995 *(CDC, 1991,CDC 1996)*. Adults who are at increased risk of HBV infection and who should receive the vaccine include: sexually active heterosexual adults with more than one sex partner in the prior 6 months or a history of a sexually transmitted disease; homosexual and bisexual men; illicit injection drug users, persons at occupational risk of infection; hemodialysis patients; and household and sex contacts of persons with chronic HBV infection; clients and staff of institutions for the developmentally disabled *(CDC, 1991 b)*.

Q. **Why is vaccination for hepatitis B required by many states for school entry?**

Without state and local immunization laws many more people would become sick or die from hepatitis B. Immunization requirements also help protect persons who are too sick to receive the vaccine. This is done by ensuring that a large number of persons are protected with vaccine which prevents transmission of hepatitis B on to others who are not protected. The enforcement of mandatory school immunization laws has significantly increased vaccine coverage (Robbins, 1981). Before hepatitis B vaccine was recommended for all children there were approximately 30,000 infants and children each year who would become infected with hepatitis B (*Margolis, 1991*). Vaccination requirements for enrollment/attendance at day care and programs like Head Start and public and private schools and colleges in the United States, are established at the State and local levels. Laws or regulations are typically enacted by State legislatures with authority granted to State and/or local health departments for rule making, monitoring and enforcement. There are no Federal laws requiring vaccinations for day care, Head Start, school or college attendance.

Rule making is usually based on immunization schedule recommendations established by nationally recognized authorities, including the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatric's (AAP) Red Book Committee. Vaccination requirements between states vary slightly but all states have requirements in some combination against diphtheria, tetanus, pertussis, measles, mumps, rubella and polio. Vaccination against *haemophilus influenzae* type b is required for attendance at day care centers and Head Start programs in most states. More states are adding requirements for vaccination against hepatitis B and varicella (chickenpox) disease to day care and/or school attendance requirements.

In every instance, such requirements have significantly reduced illnesses and death from diseases that vaccines prevent. Vaccine coverage levels are higher in school-age children and those enrolled in licensed day care centers and Head Start programs then among any other comparable group of infants, children or adolescents. These levels have been well documented at or above 95 percent in all states for many years.

Vaccination requirements for day care and school attendance are also successful in other ways. For example, children with leukemia or who suffer from problems with their immune system may not

receive some vaccines. The effect of compulsory and mass vaccination programs is to better reduce the likelihood of exposure of these children to diseases that could be life-threatening. The greater the number of children who refuse vaccination, the greater the risk of disease is to persons who can not be immunized because of health reasons. Likewise, the community benefits by having a large number of persons vaccinated and protected from disease. High coverage levels limit the introduction or spread of disease, benefiting everyone.

The 1996 ACIP recommendations on adolescent immunization is jointly endorsed by the AAP, the American Academy of Family Physicians, and the American Medical Association. The statement reads in part: "In the United States, state vaccination laws and regulations for kindergarten through grade 12 are effective in ensuring high coverage levels among school attendees and have led to a marked decline of overall morbidity and mortality from vaccine-preventable diseases. Additional state laws and regulations requiring documentation of up-to-date immunization of adolescents, or a reliable history of disease-related immunity, at entry into sixth grade would ensure implementation of these recommendations and would lead to further reduction in transmission of vaccine-preventable diseases."

Q. **Why not vaccinate children in those families where there is the highest risk of HBV infection, rather than vaccinating all infants/children?**

A. Routine immunization of infants and adolescents is recommended for several reasons. One is that there is a large disease burden attributable to HBV infections that occur among children. Approximately 30,000 infants and children were infected each year before routine infant hepatitis B immunization began and CDC estimates that one-third of the chronic HBV infections in the United States come from infected infants and young children. The majority of these infections occur among children of mothers who are not infected with HBV and thus would not be prevented by perinatal hepatitis B prevention programs. Other than for infants born to HBV infected pregnant women, there is no way to identify and selectively vaccinate those children at risk of infection (*Margolis, 1991)*.

Another reason we vaccinate infants and older children is that it will provide them protection against exposure to HBV infection when they are older adolescents and adults. While most HBV infections occur among older adolescents and young adults, vaccination of persons in high risk groups has generally not been a successful public health strategy. In addition, about 30 percent of persons do not know where they acquired their acute HBV infection *(Alter, 1990)*.

Q. **Is hepatitis B vaccine safe?**

A. Hepatitis B vaccines have been shown to be very safe when given to infants, children or adults *(CDC, 1991 a; Greenberg, 1993)*. More than 20 million persons have received hepatitis B vaccine in the United States and more than 500 million persons have received the vaccine worldwide. The most common side effects from hepatitis B vaccination are pain at the injection site and mild to moderate fever *(Szmuness, 1980; Francis, 1982; Zajac, 1986; Stevens, 1985; Andre, 1989; Greenberg, 1993)*. Studies show that these side effects are reported no more frequently among those vaccinated than among persons not receiving vaccine *(Szmuness, 1980; Francis, 1982)*. Among children receiving both hepatitis B vaccine and diphtheria-tetanus-pertussis (DTP) vaccine, these mild side effects have been observed no more frequently than among children receiving DTP vaccine alone *(CDC, 1991 a; Greenberg, 1993)*.

Whenever large numbers of individuals are vaccinated, rare reports of subsequent adverse events occur. In order to determine whether they are caused by or are just coincidental events following vaccination requires further study. Such reports do not mean that the vaccine is unsafe, since millions of persons have received the vaccine without any problem.

Q. **Is there an association between hepatitis B vaccine and serious side effects?**

A. Serious side effects reported after receiving hepatitis B vaccine are very uncommon *(Andre, 1989; CDC, 1991 a; Greenberg, 1993; Niu, 1996)*. While reported, there is no confirmed scientific evidence that hepatitis B vaccine causes chronic illness, including multiple sclerosis, chronic fatigue syndrome, rheumatoid arthritis, or autoimmune disorders. There is no risk of HBV infection from the vaccine.

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Large-scale hepatitis B immunization programs in Taiwan, Alaska, and New Zealand have observed no association between vaccination and the occurrence of serious adverse events. Furthermore, surveillance of adverse events in the United States after hepatitis B vaccination have not shown a clear association between hepatitis B vaccine and the occurrence of serious adverse events including Guillain-Barre' syndrome, transverse myelitis, optic neuritis, and seizures *(Shaw, 1988; CDC, 1991 a; Niu, 1996; Niu 1998 CDC, unpublished data)*. Additional evaluations are ongoing. A recent study suggested persons developing rheumatoid arthritis after hepatitis b vaccination were genetically at-risk for rheumatoid arthritis (*Pope, 1998*).

A low rate of anaphylaxis (hives, difficulty breathing, shock) has been observed in vaccine recipients based on reports to the Vaccine Adverse Event Reporting System (VAERS), with an estimated incidence of 1 in 600,000 vaccine doses distributed. One case has been reported in 100,763 children (10-11 years old) vaccinated with recombinant vaccine in British Columbia and no cases were observed in 166,757 children vaccinated in New Zealand. Although none of the persons who developed anaphylaxis died, anaphylactic reactions can be life-threatening, and therefore further vaccination with hepatitis B vaccine is contraindicated in persons with a history of anaphylaxis after a previous dose of vaccine. There have been rare reports of hair loss after hepatitis B vaccination, with the majority of individuals regrowing their hair (*Wise, 1997*). Studies are in progress to better quantify the possible slight risk of hair loss.

Any presumed risk of adverse events associated with hepatitis B vaccination must be balanced with the expected 4,000 to 5,000 HBV-related liver disease deaths that would occur without immunization, assuming a 5 percent lifetime risk of HBV infection.

Q. **Does hepatitis B vaccination cause demyelinating diseases such as multiple sclerosis (MS)?**

A. The scientific evidence to date does not support hepatitis B vaccination causing MS or other demyelinating diseases.

Multiple sclerosis is a disease of the central nervous system characterized by the destruction of the myelin sheath surrounding neurons, resulting in the formation of "plaques." MS is a progressive and usually fluctuating disease with exacerbations (patients feeling worse) and remissions (patients feeling better) over many decades. Eventually, in most patients, remissions do not reach baseline levels and permanent disability and sometimes death occurs. The cause of MS is unknown. The most widely held hypothesis is that MS occurs in patients with a genetic susceptibility and that some environmental factors "trigger" exacerbations. MS is 3 times more common in women than men, with diagnosis usually made as young adults.

The concern that hepatitis B vaccination may cause MS or exacerbate it derives from case reports and media attention in France and, more recently, televised news reports in the United States. However, it is possible that these MS case reports are purely coincidental to hepatitis B vaccination. Carefully controlled studies (currently underway) are needed to determine the nature of these reports.

Other than these case reports, what then is the current scientific evidence that hepatitis B vaccination causes MS or other demyelinating diseases? First, extensive pre-licensure clinical trials did not document such an effect. Second, hundreds of millions of persons worldwide have been immunized without developing MS (or any other autoimmune disease). This finding provides important negative evidence as well as an appropriate framework for assessing this possible association-namely, that if vaccination causes MS, it does so extremely rarely.

Third, prospective studies of MS patients have shown that exacerbations appeared to be more frequent after nonspecific viral illnesses *(Sibley, 1985)*. This is presumably due to generalized stimulation of the immune system that occurs with such infections *(Owen, 1980)*. There have been reports of exacerbations of MS following immunization of persons who already had MS but no evidence that vaccination increases the rate of MS in otherwise healthy persons. Given the large number of vaccinations administered worldwide, it is not surprising that surveillance systems in the U.S., France, and elsewhere *(Quast, 1991)*, have received some reports of MS temporally (coincidentally) associated with

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vaccinations. As with all such case reports, however, they only constitute signals of possible causal associations. Further controlled studies are necessary to establish causation.

A recent (and largest to date) multi-center randomized double-blind placebo controlled trial of influenza immunization in 104 MS patients failed to show any difference in attack rate or disease progression over 6 months between vaccines and placebo recipients *(Miller, 1997)*. This study suggests that even if a vaccine can exacerbate MS, it must do so only among a small minority of MS patients.

Fourth, whether vaccinations actually cause an overall excess of MS in the population (vs. being just one of multiple possible triggers for MS in genetically susceptible individuals, without causing an excess of MS) can only be evaluated in a population-based study.

Finally, MS is an autoimmune disorder in which a person's antibodies attack the body's own myelin (a sheath that covers the nerves). According to the "molecular mimicry" hypothesis, the hepatitis b vaccine must somehow be similar to the myelin in three dimensional structure thus provoking anti-myelin antibodies to form. However, recent research (as yet unpublished) using genetic sequencing has not shown a similarity between hepatitis B vaccine and myelin basic protein. This research raises doubts about the validity of the "molecular mimicry" hypothesis.

Although scientific evidence to date does not support hepatitis B vaccination causing multiple sclerosis (MS) or other demyelinating diseases, studies are currently being organized in the Vaccine Safety Datalink project at CDC and elsewhere because of public concern about this issue in France and other places and because there is little available research on this specific topic *(Chen, 1997)*. Computerized medical records on approximately 5 million or 2 percent of the U.S. population are available in this study. It will probably be at least one year, however, before any results are available

In the meantime, the concern regarding a suggested association between vaccination and MS or any other chronic illness must be weighed against the very strong evidence that vaccines have in protecting against disease and death.

Q. **Are there any studies being conducted to examine what relationship, if any, exists between the hepatitis B vaccine and multiple sclerosis (MS)?**

A. YES, there are at least six research projects underway. In recent years, several unproven theories have caused concern in the general public by suggesting there is an association between the hepatitis B vaccine and demyelinating disorders, including MS. As a result, the research studies described below were developed to investigate these hypotheses further.

The first two research projects were sponsored by the French Medications Agency, an organization similar to the United States Food and Drug Administration (FDA). One was a case-control study based on clinical reports of demyelinating disorders that were seen in 11 neurology centers across France. The second was also a case-control study. This research project was based on approximately 4 million patients receiving care through general practices in the United Kingdom. A third project was done by one of the vaccine manufacturers. Preliminary results from all three studies were shared with the French Medications Agency and the Viral Hepatitis Prevention Board in September 1998. These results are not yet available to others. If determined to be scientifically sound, these papers will be published in peer-reviewed medical journals in the near future.

The CDC's National Immunization Program (NIP) is using the Vaccine Safety Datalink (VSD) Project to examine whether there is an increased risk of MS following hepatitis B vaccination. The VSD contains data on more than 6 million people which is collected from four health maintenance organizations on the west coast. All vaccines administered within the study population are recorded. Available data include vaccine type, date of vaccination, concurrent vaccinations, the manufacturer, lot number and injection site. After vaccine administration, the medical records are monitored for potential health effects occur around the time of immunization. In this project, a case-control research design is being used to study patients 18 to 49 years of age without a prior diagnosis of MS or optic neuritis. NIP anticipates that within the study population, about 500 patients will be diagnosed with MS by a

physician using specific criteria. This study is being funded and organized by CDC in collaboration with Kaiser Permanente HMO's in Portland, Oregon, Northern California, and Southern California, and Group Health Cooperative of Puget Sound in Seattle, Washington. Research results will be available within the next few years.

Data from the Harvard Nurses Health Study (NHS) are being used to examine whether a possible relationship between hepatitis B vaccine and MS exists. NHS data collection began in 1976 and longitudinal follow-up is on-going. The study population includes a randomly selected cohort of nurses age 25-55. Researchers are using a nested case-control design with approximately 200 MS cases having been identified. Cases are being verified by follow-up questionnaires to the patient's physician as well as classification by a blinded panel of neurologists. Two control groups are being used. Every MS patient will be matched with five healthy controls and one control with a diagnosis of breast cancer (to control for recall bias). This study is being supported by Merck and results are expected during the fall of 1999.

Researchers at the University of Lyon in France are examining whether immunization (with any vaccine) increases the short-term risk of relapse in patients already diagnosed with MS. This project, known as the VACCIMUS study, employs a case-crossover design (where cases also serve as controls). The study includes 600 MS patients identified from neurology departments belonging to a network specializing in MS. Researchers will compare vaccination history in the three months prior to a relapse with a control period. This project is funded, in part, by Pasteur Merrieux Connaught and results are expected in the fall of 1999.

Q. **Does the scientific evidence support a causal link between hepatitis B vaccine and infant deaths?**

No. The National Center for Health Statistics, the primary Federal organization responsible for the collection, analysis, and report of health statistics, shows a consistent decline in new born deaths (infants from birth to 30 days of age) since 1935. Much of this decline is due to great improvements in sanitation, health care, and infectious disease control that have taken place during this time. Since 1991, infants have been receiving hepatitis B vaccine on a routine basis starting as early as the first day of life. Examination of newborn deaths during this time does not reveal any increase in reports, but continues to show a steady decrease in numbers of newborn deaths (*Kiely, 1998*). In a review of the 1991-1994 reports to VAERS, there were no unusual reports believed to be causally related to hepatitis b vaccine that occurred in infants given the vaccine were found. (*Niu et al., 1996*).

Some persons have questioned whether Sudden Infant Death Syndrome (SIDS) deaths could be related to vaccines. Several studies have looked at an association between SIDS and vaccines. The Institute of Medicine reviewed these studies and concluded that there was no evidence to prove a relationship existed between DTP and SIDS (*IOM,1991*). Almost all infants are vaccinated during the first year of life. Therefore, any infant with a medical illness or who dies is likely to have been vaccinated earlier in life. Since vaccinations are usually administered at ages 2 months, 4 months and 6 months, a statistically measurable chance of any event, death or otherwise, can occur within 24 hours of vaccinations by coincidence alone (*AAP, 1995*). Medical scientists have no convincing evidence or proof that there is a connection between SIDS and vaccines. In fact, deaths from SIDS have been decreasing in the past few years (*Willinger et al., 1998*). If SIDS were some how related to hepatitis B vaccines we would expect to see an increase in SIDS deaths since 1991 after hepatitis B vaccine was recommended for all infants. A few years ago some people had questioned whether the Diphtheria, Pertussis, Tetanus (DPT) vaccine was somehow related to SIDS deaths. In one study, scientists examined data from the National Institute of Child Health and Human Development's, Sudden Infant Death Syndrome Cooperative Epidemiological Study. The results confirmed earlier preliminary findings that DTP immunization was not a key factor in the occurrence of SIDS (*Hoffman et a., 1987*). In another analysis of the question looking at VAERS data scientists determined how many cases of SIDS would be expected to occur around the time a DPT vaccine is given based on chance alone. Based on birth and immunization rates, and the incidence of SIDS, scientists expected approximately 34 cases of SIDS to occur within 24 hours of receipt of DPT vaccine based purely on chance. Therefore 34 cases of SIDS would be expected to be reported to the Vaccine Adverse Event Reporting System unrelated to the vaccine but occurring around the time DPT vaccine was given. The average number of observed reports of all deaths, not just SIDS,

within 24 hours of DTP reported to the Vaccine Adverse Event Reporting System was 22 reports for the year the analysis took place (*AAP, 1992*). Today more is understood about the cause of SIDS. Recent evidence shows that babies who are positioned on their stomach have a greater risk of SIDS. Scientists believe that this sleeping position may interfere with the babies ability to breathe properly resulting in the increased risk of SIDS death (*AAP, 1992*).

Q. **How is vaccine safety monitored after it is licensed for use?**

A. The Vaccine Adverse Event Reporting System (VAERS) ensures the safety of vaccines distributed in the United States. VAERS reports are usually submitted by health care professionals or vaccine manufacturers, however anyone can submit a report to VAERS. VAERS is administered, monitored and analyzed jointly by the CDC and FDA. Persons who wish to report a possible health effect related to a vaccine should notify their health care provider and can also call the VAERS program at 1-800-822-7967.

Q. **Can the Vaccine Adverse Event Reporting System (VAERS) be used to determine the number of side effects that occur after people receive hepatitis B vaccine?**

A: No. There are several reasons why numbers of cases from VAERS can not be used to determine numbers of side effects that occur after people receive vaccines. First, VAERS accepts all reports of adverse health events which follow vaccination regardless of the cause. Therefore VAERS contains a mix of vaccine-caused side effects and health effects not related to vaccines. Second, the same case may be reported to VAERS more than once. This can happen when different people file the same report. For instance, a health care provider, a parent and a manufacturer may all send VAERS the same report resulting in several entries of the same case into the data base. Other reports are filed more than once because vaccines are typically given in combination with other vaccines so the same report may be filed separately under each vaccine. Reports are also filed separately from the same case under each adverse effect listed. For instance, one report that listed fever and headache and persistent crying would be filed separately into the system under each health effect reported. In addition the details and diagnosis of a given report may be incomplete or inaccurate depending on a person's access to complete clinical information. Without fully understanding these and other limitations, VAERS data can easily be misinterpreted or analyzed incorrectly leading to false conclusions about reports of health effects occurring after vaccine administration. (*Chen et al., 1994; Ellenberg et al., 1997*).

Serious health events reported to VAERS, such as reports of death, are followed up by VAERS staff. Autopsy and death certificate records are requested and reviewed for each death report. Follow up for other serious reports is done to collect additional clinical information including recovery status. The vast majority of death reports to VAERS are later determined not to be related to vaccines.

Scientists use VAERS data to look at overall trends or unusual occurrences. In a review of the 1991-1994 reports to VAERS, no unusual reports felt causally related to hepatitis b vaccine occurred in infants given the vaccine were found. (*Niu et al., 1996*). Of the 12 million doses of hepatitis B vaccine given in these age groups, the vast majority reported no side effects. Another study reviewed preliminary VAERS data which at first suggested that more severe adverse events may occur in children receiving one brand of hepatitis B vaccine, however further analysis found that this was false and not a true difference. This study showed some of the problems involved with interpreting VAERS data (*Niu et al., 1998*).

In addition, data from the National Center for Health Statistics, the primary Federal organization responsible for the collection, analysis, and reports of health statistics, show a consistent decline in new born deaths (infants from birth to 30 days of age) since 1935. Much of this decline is due to great improvements in sanitation, health care, and infectious disease control that have taken place during this time. Since 1991, infants have been receiving hepatitis B vaccine on a routine basis starting as early as the first day of life. Since 1991, infants have been receiving hepatitis B vaccine on a routine basis starting as early as birth. Examination of newborn deaths during this time does not reveal any increase in reports, but continues to show a steady decrease in numbers of newborn deaths (*Kiely, 1998*).

Q. **Where can I find more information about hepatitis B and hepatitis B vaccine?**

Further information regarding hepatitis B and hepatitis B vaccine can be obtained by contacting the Hepatitis Hotline of the Hepatitis Branch, CDC at 1-888-4HEP-CDC (or 1-888-443-7232) and by contacting your local or State health department. For information about vaccines contact the National Immunization Program, CDC Information Hotline at 1-800-232-2522 (English) or 1-800-232-0233 (Spanish);or visit the CDC National Immunization Program website at http:/www.cdc.gov/nip, or the CDC Hepatitis Branch web site at http://www.cdc.gov/ncidod/diseases/hepatitis/hepatitis.htm

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**References**

Advisory Committee on Immunization Practices (ACIP). Vaccines for Children Program: Resolution No. 10/97-1. Adopted October 23, 1997, Effective March 1, 1998.

Alter MJ, Hadler SC, Margolis HS, et al. The changing epidemiology of hepatitis B in the United States. Need for alternative vaccination strategies. JAMA 1990;263:1218-22.

American Academy of Pediatrics AAP. Positioning and SIDS AAP task force on infant positioning and SIDS. Pediatrics. 1992,89:1120-1126.

Andre FE. Summary of safety and efficacy data on a yeast derived hepatitis B vaccine. Am J Med. 1989;87(Suppl 3A): 14s-20s.

Centers for Disease Control and Prevention. Protection against viral hepatitis: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 1990;39:5-22.

Centers for Disease Control and Prevention. Hepatitis B virus: A comprehensive strategy for eliminating transmission in the United States through Universal Childhood Vaccination. MMWR. 1991;40 (RR-13):1-17.

Centers for Disease Control and Prevention. Immunization of adolescents: Recommendations of Advisory Committee on Immunization Practices, American Academy of Pediatrics, American Family Physicians and American Medical Association.. MMWR. 1996; 45 (RR-13):1-14.

Centers for Disease Control and Prevention. Update on Adult Immunization: Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR. 1991;40 (RR-12);30-33.

Chen D-S. Control of hepatitis B in Asia: mass immunization program in Taiwan. In: Hollinger FB, Lemon SM, Margolis HS, eds. Viral hepatitis and liver disease. Baltimore: Williams and Wilkins, 1991:716-719.

Chen RT, Glasser J, Rhodes P, et al. The Vaccine Safety Datalink Project: A New Tool for Improving Vaccine Safety Monitoring in the United States. Pediatrics 1997;99:765-73.

Chen RT, Rastogi SC, Mullen JR, Hayes S, Cochi SL, Donlon JA, Wassilak SG. The Vaccine Adverse Event Reporting System (VAERS). Vaccine 1994;12:542-50.

Ellenberg SS, Chen RT. The complicated task of monitoring vaccine safety. Public Health Reports 1997;112:10-20.

Emini EA, Eliis RW, Miller WJ, et al: Production and immunologic analysis of recombinant hepatitis B vaccine. J infect. 1986;13 (Suppl A):3-9.

Francis DP, Hadler SC, Thompson SE, et al. Prevention of hepatitis B vaccine: report from the Centers

2-12

for Disease Control multi-center efficacy trial among homosexual men. Ann Intern Med. 1982;97:362-6.

Greenberg DP. Pediatric experience with recombinant hepatitis B vaccines and relevant safety and immunization studies. Pediatr Infect Dis J. 1993;12:438-445.

Hadler SC, Margolis HS. Hepatitis B Immunization: vaccine types, efficacy, and indications for immunization. In: Remington JS, Swartz MN, eds. Current Clinical Topics in Infectious Diseases. Boston Mass: Blackwell Scientific Publications; 1992:282-308.

Hoffman HC, Hunter JC, Damus K et al. Diphtheria-tetanus-pertussis immunization and sudden infant death: results of the National Institute of child health and human development cooperative epidemiological study of sudden infant death syndrome risk factors. Pediatrics. 1987 Apr;79(4):598-611.

Humiston S, Atkinson W. 1998 immunization schedule changes and clarifications. Ped Annals. 1998; 27(6): 338-48.

Kiely, J. National Center for Health Statistics, Presentation at the Vaccine Safety Froun October 26th 1998 Washington DC.

Margolis HS, Alter MJ, Hadler SC. Hepatitis B: evolving epidemiology and implications for control. Semin Liver Dis. 1991;11:84-92.

Miller AE, Morgante LA, Buchwald LY et al. A multi center, randomized double-blind placebo controlled trial of influenza immunization in multiple sclerosis. Neurology 1997:48:312-314.

Niu MT, Davis DM, Ellenberg S. Recombinant hepatitis B vaccination of neonates and infants: emerging safety data from the Vaccine Adverse Event Reporting System. Pediatr Inf Dis J 1996;15:771-6.

Niu MT, Rhodes P, Salive M, Lively T, et. al. Comparative safety data of two recombinant hepatitis B vaccines in children: data from the Vaccine Adverse Event Reporting System (VAERS) and Vaccine Safety Datalink (VSD). J Clin Epidemiol 1998;51:503-10.

Owen RL, Dau PC, Johnson KP, Spitler LE. Immunologic mechanisms in multiple sclerosis: exacerbation by type A hepatitis and skin test antigen. JAMA 1980;244:2307-2309.

Pope JE, Adams S, Howson W, et al. The development of rheumatoid arthritis after recombinant hepatitis b vaccination. J Rheumatol 1998; 25: 1687-93.

Poser CM. Notes on the pathogenesis of multiple sclerosis. Clinical Neuroscience 1994;2:258-265.

Quast U, Herder C, Zwisler O. Vaccination of patients with encephalomyelitis disseminata. Vaccine 1991;9:228-230.

Robbins KB, Brandling-Bennett AD, Hinman AR. Low measles incidence association with enforcement of school immunization laws. Am J Pub Health. March 1981; 71(3): 270-274.

Shaw FE, Graham DJ, Guess HA, et al. Postmarketing surveillance for neurologic adverse events reported after hepatitis B vaccination. Am J Epidemiol. 1988;127:337-352.

Sibley WA et al. Clinical viral infections and multiple sclerosis. Lancet 1985;1:1313-1315.

Stephenne J. Development and production aspects of a recombinant yeast-derived hepatitis B vaccine. Vaccine. 1990;8:S69-73.

Stevens CE, Toy PT, Tong MJ, et al. Perinatal hepatitis B virus transmission in the Unites States: prevention by passive-active immunization. JAMA. 1985; 253:1740-1745.

2-13

Strom BL, ed. Pharmacoepidemiology. Sussex: John Wiley & Sons, 1994.

Szmuness W, Stevens CE, Harley EJ, et al. Hepatitis B vaccine: demonstration of efficacy in a controlled clinical trial in a high risk population in the United States. N Engl J Med. 1980;303:833-841.

West DJ, Margolis HS. Prevention of hepatitis B virus infection in the United States: a pediatric perspective. Pediatr Infect Dis J. 1992;11:866-874.

Willinger M, Hoffman HJ,Wu KT et al. Factors associated with the transition to nonprone sleep positions of infants in the united states, the national infant sleep position study. JAMA. 1998: 280:329-335

Wise RP, Kiminyo KP, Salive ME. Hair loss after routine immunizations. JAMA. 1997;278:1176-1178.

Zajac BA, West DJ, McAleer WJ, Scolnick EM. Overview of clinical studies with hepatitis B vaccine made by recombinant DNA. J Infect. 1986;13(Suppl A):39-45.

**For additional reference**

World Health Organization. Scare of multiple sclerosis from hep B vaccine "quite unfounded". Vaccine and Immunization News: The newsletter of the global programme for vaccines and immunization, World Health Organization. 1997; No. 4: p. 8.

World Health Organization. No evidence that hepatitis B vaccine causes multiple sclerosis. Weekly Epidemiological Record, World Health Organization. 1997; No. 21: pp. 149-152.

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Vaccine Safety and Development Activity

Last Updated February 1, 1999

**TESTIMONY**
**Before the Senate Committee on Public Health and Welfare**
**February 2, 1999**

**Carol Cowden**
**Immediate Past Director, Mid America Immunization Coalition**

Senators, thank you for the opportunity to speak on behalf of a requirement to immunize middle-schoolers against hepatitis B.

I am Carol Cowden, until a few months ago, the director of the Mid America Immunization Coalition in metropolitan Kansas City. One of the most valuable projects we have undertaken in our area is our school-based immunization program. Begun three years ago as a small pilot project in two Kansas City middle schools, we have now nearly completed two additional years of immunizing 11 and 12 year olds against hepatitis B. This year we are providing the three dose series of hepatitis B vaccine in 23 school districts and 55 private schools – all free of charge. Local health department nurses with the help of hospital nurse volunteers are giving the shots.

We started out with seed money from Merck Vaccine Division as well as funding help from area managed care companies, foundations and other private funders. Last March, the State of Missouri provided funding so that all Missouri children infancy through age 18 could receive the shots at no cost; thereby covering the vaccine cost of immunizing all Kansas City, Missouri children in our program. It is our hope that Kansas 11 year olds will receive the same coverage next year.

The program has been extremely popular in Kansas City. School officials are eager for these services; parents are happy to have their early adolescents protected against a potentially dangerous disease and in such a convenient way; and all of our community partners seem delighted with the efficiency and efficacy of the program.

Why did we choose to offer hepatitis B shots to 11 and 12 year olds?

Aside from the fact that it is a recommendation of the CDC, the American Academy of Pediatrics, and the American Academy of Family Physicians, we have discovered that: adolescents are particularly vulnerable to hepatitis B as they begin to participate in activities that can spread the disease, including sharing toothbrushes, cups or razors, coming in contact with an infected person's blood in sport injuries, receiving tattooing or body piercing services, engaging in unprotected sexual intercourse, and sharing needles during drug use.

Choosing to "catch up" 11 and 12 years olds allows us to protect these children before the riskier activities of the teen years begin. A large cohort of children who received hepatitis B shots at birth is rising through the elementary schools. In a few years, when these children become 11 and 12 year olds, we can cease our targeting of this age level because an very high percentage will have been immunized at birth. Having a large number of children and adolescents vaccinated against this insidious disease will not only protect our children, but also go a long way to eliminate transmission of hepatitis B in the United States. We encourage you, therefore, to allot the appropriate funding for a school entry requirement of hepatitis B for middle school students.

Thank you.

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*February 2, 1999*

# HEPTITIS B FOR ADOLESCENTS IN KANSAS

*WRITTEN TESTIMONY*

Chairperson Praeger and members of the Senate Public Health and Welfare Committee, KANSAS STATE NURSES ASSOCIATION asks for your consideration and support of fostering Hepatitis B Vaccine for adolescents in Kansas for the academic year beginning August 1999. KSNA is pleased to join with todays sponsors to bring you the most up to date information about Hepatitis B, the vaccine available to reduce exposure and incidence of Hepatitis B, and effective mechanisms for vaccinating adolescents.

In our state, infant, adolescent, and adult immunizations play an important role in disease prevention and reduction. KSNA has been instrumental in promoting the early childhood vaccine endeavors in Kansas the past seven years through Operation Immunize, and ongoing activities to heighten the publics awareness of the benefits to timely age-specific immunizations. Although no vaccine is perfect, the benefits of immunization far outweigh the risks. Thanks to vaccines, fewer cases of vaccine-preventable disease were reported in the U.S. in 1998 than in any previous year. Recent changes in the nation's vaccine recommendations have made immunizations even safer.

There are numerous resources available for health professionals, particularly registered nurses to become proficient regarding the need for and strategies for immunizing adolescents against Hepatitis B. KSNA has begun dissemination of these to the more than 25,000 registered nurses in the state and will be prepared to facilitate greater and wider information dissemination if a state policy is implemented to vaccinate adolescents against Hep. B. Registered Nurses are committed to disease prevention and health promotion and we will work with our public health partners and appointed leaders towards continued success in immunization promotion.

Thank You for Your Supr




Senate Public Health and Welfare
Date: 2-2-99
Attachment No. 4

JOURNAL OF ADOLESCENT HEALTH 1995;17:234–243

REVIEW ARTICLE

# Hepatitis B Immunization in Adolescents

MONIQUE H. LAWRENCE, S.B., AND MARK A. GOLDSTEIN, M.D., F.S.A.M.

**This article reviews the epidemiology of hepatitis B in the United States, previous vaccination strategy, and reasons for its failure and issues leading to the recommendation to vaccinate all adolescents. A review of specific hepatitis B virus risk behaviors of adolescents and barriers to vaccinating adolescents is covered. Strategies that favor successful completion of the immunization series are also examined. Hepatitis B infection is an important public health concern for adolescents. The previous vaccine strategy to immunize only individuals thought to be at high risk was unsuccessful, especially because providers of care could not identify these individuals. Furthermore, many individuals thought not to be at high risk for infection were exposed through contacts which could not be identified. Challenges to immunization of adolescents include logistical issues, patient education, cost of the vaccine, and patient compliance. Several of these issues can be addressed by a school-based hepatitis B immunization program. The body of evidence and national policy is rapidly changing to support the recommendation that all adolescents receive the hepatitis B immunization series. The series would be most effective if administered during the middle-school years. A universal adolescent hepatitis B vaccination program would result in the most immediate health benefits and acceleration toward the eradication of hepatitis B in the United States.**

KEY WORDS:
Hepatitis B
Hepatitis B immunization
Adolescents
Prevention
Immunization

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*Manuscript accepted June 16, 1995.*

Hepatitis B is one of the most prevalent infectious diseases in the world. Globally, it has been estimated that over 300 million people, more than 5% of the world's population, are chronically infected with hepatitis B (1–3) and over 250,000 people die each year of hepatitis B–associated acute and chronic liver disease (3). The hepatitis B virus (HBV) is a potent carcinogen, and all chronic carriers are at risk of developing hepatocellular carcinoma (4). Chronic HBV infection is estimated to be the etiologic agent for 75–90% of all primary liver cancers worldwide (4); in many highly endemic areas, hepatocellular carcinoma is the most common neoplasm (5). HBV endemic areas include most of Africa, the Pacific Islands, all of Southeast Asia and China, parts of the Middle East, and the Amazon Basin. In these areas, chronic HBV infection usually results from contact with HBV during early childhood through perinatal transmission (6,7) or through close household contact (7,8).

Although the United States is not an HBV endemic area, serologic studies show that as much as 5% of the U.S. population has been infected with the virus (9). Most infections in the United States occur among adolescents and young adults (10) through sexual contact and intravenous drug use (11,12). It is estimated that 300,000 HBV infections occur annually in the United States (13,14), resulting in 20,000 chronic infections and over 4000 deaths (15) due to cirrhosis, acute fulminant hepatitis, or liver cancer (12,13). In the United States, the fatality rate owing to hepatitis B had surpassed all other preventable diseases prior to the implementation of universal immunization programs (400–500 deaths/year from measles and 800–1000 deaths/year from *Hemophilus influenzae* type B infection) (16,17). The economic burden of HBV was estimated to be approximately over $200 million in 1970 (18).

A safe and effective vaccine to prevent HBV

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infection was licensed in the United States in 1982, but despite its availability for over a decade, the incidence of HBV infection in the United States has increased by 37% (19). The paradoxical increase of HBV infections since the introduction of the vaccine is due to the limited scope of the previous vaccination strategy that targeted select high-risk groups including IV drug abusers and persons exposed to HBV infection through sexual or household exposure.

The Immunization Practices Advisory Committee (ACIP) of the Centers for Disease Control and the American Academy of Pediatrics (AAP) revised their guidelines to recommend universal immunization of all infants (19,20). The benefits of infant vaccination, however, will not be seen until the vaccinated cohort reach an age where they might engage in activities that put them at risk for HBV infection. Routine vaccination of adolescents is not currently required, in large part because of the financial (21) and logistical (20) obstacles of such a widespread undertaking. Instead, the ACIP and AAP recommend targeted vaccination for adolescents who display increased risk of infection and universal adolescent immunization in communities with high rates of IV drug use, teenage pregnancy, and sexually transmitted diseases (STDs) (19,20). To reduce the transmission of HBV most rapidly, the AAP stresses the need to vaccinate all children before or during adolescence as soon as resources permit (22).

Universal vaccination of infants alone would have virtually no impact on the disease prevalence for 15 to 20 years, because for most children in the United States, the risk of HBV infection remains low until adolescence (22). Only approximately 8% of acute infections in the United States occur in children younger than 10 years (12). If the current cohort of children and adolescents remains unimmunized, many will continue to be at risk for HBV infection for several decades after the initiation of universal immunization of all infants (22).

This commentary reviews the epidemiology of hepatitis B in the United States, previous vaccination strategy and reasons for its failure, and issues leading to the recommendations to vaccinate all adolescents. Specific HBV risk behaviors of adolescents and obstacles to vaccinating adolescents are covered. This review also outlines strategies that favor successful completion of the three-dose immunization series, including school-based undertakings. Issues concerning indications for vaccination, patient compliance, patient access, and vaccination cost are also addressed.

## *Background*

Hepatitis B is an important public health concern because of its infectiousness, the various routes by which it can be transmitted, and the difficulty in identifying infection through specific clinical symptoms. HBV is present in blood and blood products, saliva (23,24), semen (24), vaginal secretions (25), and wound exudates. The hepatitis B virus is very stable. It can survive up to 1 week in dried blood (22) and is considerably more infectious than HIV. Persons who have close contact with blood and blood products, such as health care workers, hemodialysis patients, and IV drug users, are at risk of infection. HBV transmission through sexual contact is a major route of transmission among the male homosexual population (26–28) and is increasing among the young heterosexual population (11). HBV can be transmitted through close household contact such as sharing razors and toothbrushes (29). Children can transmit the virus to one another through close physical contact such as bites, scratches, or open skin lesions (30).

HBV infection often goes undetected because more than 50% of infections in adolescents and adults are asymptomatic (10,15,31,32). If symptoms do develop, the onset is generally insidious. Many persons experience illness so mild that they do not seek medical attention, or if they do, a diagnosis of hepatitis B is not considered (9,31).

Individuals with acute HBV infection are potentially infectious to others during the course of their infection (<6 months). Chronic carriers are at the heart of the public health concern, because they are potentially infectious to others during their entire lifetime. A variable proportion of infected individuals will become chronic carriers, and the likelihood of developing chronic infection varies inversely with age; between 25 and 50% of children infected before 5 years of age become carriers, whereas 6–10% of acutely infected adults become carriers (13). There are an estimated 1–1.25 million chronic carriers in the United States (19), many of whom may not know they were initially infected, have developed a subsequent carrier state, and are now potentially infectious to others.

Most adults with acute hepatitis B infections recover, with a 1% incidence of fulminant liver disease and death (33). Although no specific treatment exists for acute hepatitis B infection, liver transplants can be performed for patients who have fulminant hepatitis B. Treatment for chronic infection is expensive and is only partially effective (33).

### *Previous Vaccination Strategy and Reasons for Failure to Reduce Incidence of HBV Infection*

The failure of the vaccine to decrease the prevalence of hepatitis B infection is attributed to several factors. The previous immunization strategy for prevention of hepatitis B in the United States was to immunize groups considered to be at high risk for infection (13). Vaccination programs and vaccine usage focused on three risk groups: health care workers exposed to blood, staff and residents of institutions for the developmentally disabled, and staff and patients of hemodialysis units (14). It is estimated that these groups received >85% of the vaccine administered, yet they accounted for only 5 to 10% of acute hepatitis B cases (14). The risk groups that accounted for most of the cases (e.g., IV drug users, homosexual men, and persons acquiring the disease through heterosexual exposure) were not effectively reached (12,14,34). These groups were not vaccinated as a result of a variety of factors, including inaccessibility, noncompliance, lack of vaccination programs, and the inability to identify persons at risk (11,12,35). Furthermore, because over 30% of HBV-infected individuals show no identifiable risk factor for infection (11), they could not even theoretically be included in a target immunization strategy.

Persons exposed to HBV infection through household contact often cannot identify their source of infection or the route of transmission. Most persons with heterosexual exposure cannot identify their source of infection, because infection resulted from exposure to multiple partners or exposure to a contact with subclinical infection (11).

The failure of health care providers to recognize high-risk patients also contributed to the ineffectiveness of the previous HBV immunization strategy (34). Providers are often not aware of groups at high risk for HBV infection and frequently do not identify candidates for vaccination during routine visits (19). A survey conducted in 1985 by the Centers for Disease Control showed that 70% of physicians indicated IV drug abusers as a high-risk group for HBV infection, whereas only 45% identified homosexual men, and very few (10%) identified heterosexuals with multiple partners or heterosexual contacts of carriers (12%) (34). Furthermore, it is unknown whether the medical care providers who are aware of high-risk groups routinely obtain a history detailed enough to identify high-risk behavior (34,36,37).

### *Epidemiology*

The majority of acute hepatitis B cases occur in three groups: IV drug abusers, homosexual men, and persons acquiring disease through heterosexual exposure (38). The rates of HBV infection vary greatly among racial and ethnic groups. Among adolescents and adults in the United States, the incidence of HBV in nonwhite racial/ethnic groups is almost twice that in whites (11). The prevalence of chronic HBV infection is 5–30 times higher among blacks and Asians compared with whites (12). Of the >30% of patients who show no identifiable source for infection, most belong to minority populations and low socioeconomic status (11,39).

The incidence of HBV infection increases rapidly during adolescence, with higher rates among blacks than whites (9). A population-based study showed that blacks start to have an increased prevalence of HBV infection by 12 years of age, whereas whites begin to show an increase at 15 years of age. Within that age range, blacks demonstrate a 3–6-fold higher incidence of HBV infection (9). Racial differences in rates of HBV infection parallel racial differences in rates of sexual activity, which may explain the earlier rise in hepatitis B incidence in black adolescents (9,40).

Several epidemiologic features set adolescents apart from adults. In contrast to adults, for whom the male to female ratio of HBV infection is 2:1, adolescent females outnumber males 1.4:1 (12). Relatively higher rates of HBV infection in adolescent females may indicate their greater physiologic vulnerability than adult females to STDs. A total of 60% of adolescents have no known source for their infections, compared with 30% of infected adults (12). Of the cases of HBV infection in adolescents with a known source of infection, 50% can be attributed to sexual or other person-to-person contact, and 47% to IV drug use (12).

Alter et al. conducted intensive surveillance from 1981 to 1988 of U.S. sentinel counties with rates of HBV infection representative of many areas in the United States (11). During this period, the rate of infection owing to homosexual activity and health care employment declined dramatically (62 and 75%, respectively), whereas that due to heterosexual exposure and IV drug use increased 38 and 80%, respectively (11). Whereas previously, HBV transmission through sexual contact was mainly associated with homosexual activity (26–28), now heterosexual exposure (including sexual contact with

infected persons or with multiple sexual partners) is a more important risk factor (11).

The decrease of HBV infection among health care workers is largely the result of immunization with hepatitis B vaccine and wider implementation of universal blood precautions (11). The decrease among the homosexual male population is attributed to behavioral changes to reduce the risk of acquiring human immunodeficiency virus (HIV) (11,41–48); few individuals in this risk group had actually been vaccinated, because of a lack of programs (12).

Recent studies suggest that many adolescent and young adult homosexual and bisexual men are not as concerned about HIV risks as are older homosexual and bisexual men. Adolescent and young adult homosexual and bisexual men continue to engage in unprotected anal intercourse (49–51), report higher levels of unsafe sexual behavior than do older homosexual and bisexual men (49,52–54), and continue to become infected with HIV (51,55) with infection rates highest among African-American homosexual and bisexual men (51).

Modification of high-risk behavior in the face of AIDS is also less common in heterosexual adolescent and young adult populations (44,56–61), as is risk reduction among urban minorities (44,62). Although some studies indicate a reduction in high-risk sexual behavior by adolescent males (63) and urban minorities (63) in response to concern about contracting HIV, many other studies show that the sexual behavior of adolescents (56,58,59,61–66) and college students (60,67) is not changing dramatically despite increased knowledge about the health risks associated with high-risk sexual practices.

The rate of HBV infection among IV drug users has increased (11), but some data are promising. To reduce the risk for acquiring HIV, IV drug users show an increase in demand for new, unused needles, an increase in needle sterilization (44), and a decrease in needle sharing (44). Although needle exchange programs have shown success (68,69), needle exchange is illegal in 11 states and some cities.

### *HBV Risk Behavior of Adolescents*

The increased risk of acquiring HBV infection is associated with an increased number of sexual partners (70), increased number of years of sexual activity, and history of other sexually transmitted diseases (39,71–74). Heterosexual activity among U.S. adolescents has increased dramatically since the 1970s (63,70,75). In 1970, 4.6% of 15-year-old girls were sexually experienced, in contrast to 1988, when 25.6% were sexually active (70). The national school-based 1991 Youth Risk Behavior Survey sampled students in all public, private, and parochial schools from grades 9 to 12 to measure health risk behaviors among adolescents (76). Among all students, greater than half had participated in sexual intercourse and almost one-fifth had four or more sexual partners in their lifetime (76,77). Among the students who engaged in sexual intercourse, almost 70% were currently sexually active (within 3 months preceding the survey), and fewer than half had used a condom during their most recent sexual intercourse (76). The prevalence of these behaviors is probably underestimated for the total adolescent population, because adolescents who do not attend school were not sampled, and delinquent youths show marked increases in many HBV risk behaviors (78). The high rates of STDs (79,80) and pregnancy (80,81) in the adolescent population confirm that many adolescents engage in unsafe sexual practices (82). One in eight adolescents is diagnosed with an STD (83). Among sexually active individuals of all ages, 15–19-year-old adolescents have the highest rates of gonorrhea, syphilis, cervicitis, and hospitalizations for pelvic inflammatory disease (PID) (84–86). Adolescents are at higher risk for certain STDs than are persons in other age groups (87) as a result of increased cervical columnar epithelium which is less resistant to chlamydial and gonococcal infection and a relatively unchallenged immune system, because they are less likely than older persons to have been exposed to an STD. Adolescents who have STDs such as herpes, chancroid, and syphilis may be more susceptible to infection because of open genital lesions.

Studies show that as adolescents age, they increase their level of sexual activity and decrease their condom use (88). Use of birth control pills is higher among older than younger adolescents. These findings suggest that although the older group were better protected against unintended pregnancy, they were less protected against acquiring STDs such as hepatitis B.

High-risk individuals may engage in high-risk behaviors. Many injecting drug users share needles and other equipment, trade sex for drugs, and have unprotected sex with numerous partners (89–91). Youth at the highest risk are often homeless and/or runaways, school dropouts, youth offenders, injection drug users, or users of crack cocaine, and therefore may be especially difficult to reach. Alcohol and other noninjection drug use can precede several risk behaviors such as unprotected sex (51,88) larger

number of partners (88), and increased frequency of intercourse (88).

Human immunodeficiency virus and AIDS-reduction research has determined that adolescents are likely to be the most difficult age group to influence toward prevention, largely because of their susceptibility to negative peer pressure, propensity to take risks including sexual and drug experimentation, sense of invulnerability and immortality, and difficulty grasping the long-term adverse consequences of current behavior (92–96). Because the prevalence of hepatitis B infection significantly increases at ages when adolescents begin to experiment with sex and drugs, preventive intervention beyond education and counseling is crucial, and administration of the HBV vaccine is warranted.

### *Adolescent Vaccination Strategy*

Adolescents represent a unique challenge for vaccination. First, the immunization schedule requiring administration of three doses of vaccine over a 6-month period poses certain logistical difficulties. Adolescents are often noncompliant with appointments (97), and successful completion of the immunization scheme may require extra effort to promote compliance. Fitting the three-dose regimen into the academic year favors vaccination provided through school-based clinics or school-wide efforts, although few such extensive undertakings exist (98,99). Thus, the health care provider may have to start the three-dose schedule for many individuals at different times in the academic year. The feasibility for completion of the three-dose regimen (22) around school vacations, examination periods, and so forth should be considered. The 0-1-6-month schedule is recommended for vaccinating adolescents with the age-specific dose of the vaccine (Table 1) (19). The dosage of Engerix-B for adolescents ages 11–19 for the usual dosing schedule of 0-1-6 months previously was 20 μg/dose; the current recommendations are either 10 or 20 μg/dose. Geometric mean titers 1–2 months after completion of the three-dose series (0-1-6 months) are higher for patients receiving the 20 μg dosage, but seroprotection rates are similar for both groups (100).

The AAP recommends that all adolescents be immunized against hepatitis B (22), and the ACIP is currently drafting recommendations for universal adolescent immunization. Pediatric and adolescent health care providers should regard each patient as currently or potentially at risk for HBV infection. For adolescents, a thorough sexual history should be taken including past sexual experiences. Beside the AAP, others advocate that all sexually active young adults be targeted for vaccination (99). Until the financial resources allow for universal vaccination, at the very least, a target strategy to vaccinate adolescents who demonstrate high-risk behavior is recommended. Until such time as universal immunization is accomplished, the AAP recommends that special efforts be made to vaccinate adolescents who: (a) have sexually transmitted disease(s), (b) have had more than one sexual partner in the previous 6 months, (c) are IV drug users, (d) are sexually active homosexual or bisexual males, (e) are sexual contacts of high-risk individuals, or (f) may have occupational exposure to blood or blood-contaminated body fluids. Immunization should be emphasized for adolescents living in areas where increased rates of IV drug abuse, teenage pregnancy, and/or sexually transmitted diseases occur (20). Requests for oral contraception may be an indication for vaccination, because the use of barrier methods of contraception is low among adolescent users of oral contraceptives (101–103). The health care provider must be skilled in eliciting a personal history detailed enough to identify high-risk behavior, and must convey the importance of receiving the vaccine for those who demonstrate high risk for infection.

Adolescents at highest risk would most likely be least compliant, and asking adolescents to participate in a three-dose immunization series over a 6-month period is likely to result in high dropout rates (20). The health care provider may employ several methods to promote successful completion of the three-dose schedule in this group. Studies show that adolescents are more prone to keep appointments if they feel they are susceptible to infection (104,105), realize appointments are for treatment purposes (106), and understand the negative consequences of not adhering to the regimen (107). The health care provider may discuss the negative consequences of no or incomplete vaccination such as the danger of acute infection; the slim, yet real chance of becoming a chronic carrier; the limited success, high cost, and significant morbidity of the current treatment for chronic carriers; and the likelihood of developing life-threatening liver complications if chronic infection develops.

Adolescents may think they are immune from infection after just one dose of vaccine and may miss or break appointments for subsequent doses. The health care provider should stress that three doses are needed for optimal protection, and it is the third

dose in particular that markedly increases the vaccine's protective capacity (108).

Adolescents will be more compliant with appointment keeping if it is understood that the return appointments are for treatment rather than a nontherapeutic procedure such as screening (106, 109,110). A recent study showed that although prevaccination screening may be cost-effective for some high-risk groups, the additional office visit required for prescreening lowers the completion by 22% (111) as well as increases the costs for the entire series.

Clinic-specific factors that lower broken appointments include appointment reminders such as mailed or telephone reminders (112), appointments with the same physician to promote a sense continuity of care and order (97,112,113), and appointments at specific times (112) to limit long waiting times (105,114,115).

Although preexisting health services are not necessary to carry out vaccination (98), the presence of a school clinic may facilitate such programs (98). In a school setting, the vaccine can be coordinated with educational and motivational approaches to encourage student participation (98). Peer counseling services can be used through schools, and is being used in some settings including universities to promote vaccine use and compliance by students. In addition, school-based health personnel can provide follow up for students who do not return consent forms or miss vaccine doses (98). Currently more than 500 school-based clinics are believed to exist. Hepatitis B vaccination programs for adolescents and preadolescents in schools and other settings have been conducted from 1992 to 1994 in California, Louisiana, and Oregon (98). The vaccine was made available on a free and voluntary basis in all instances. Between 82 and 95% of individuals completed the three-dose schedule.

Because the least accessible adolescents may be the most at risk (116), special efforts must be made to reach adolescents not attending school. In Oregon, adolescents at high risk for infection were accessible through juvenile detention centers, school-based primary care clinics, residential facilities for psychosocially dysfunctional children, and family planning and STD clinics (98). To reach more adolescents at risk, the vaccine should also be made available through drug outreach and treatment programs.

## *Vaccines*

Two hepatitis B vaccines, Recombivax HB and Engerix-B, are currently available in the United States (19). Both are produced by recombinant DNA technology (19) and appear to be equally immunogenic (20). They may be used interchangeably in their respective recommended doses (20) (Table 1). The vaccination schedule most used for adults and children has been three intramuscular injections, the second and third administered 1 and 6 months respectively, after the first (19).

Side effects of the vaccine are rare and, if present, are minimal, consisting primarily of soreness at the injection site. Prevaccination serologic testing is generally not cost-effective or indicated except in the cases of high-risk adolescents such as IV drug users and male homosexual or bisexual teenagers (22), or persons from hepatitis B endemic countries, particularly Southeast Asia (111). Immunizing an individual previously exposed to the virus apparently causes no adverse effects (117). However, these individuals should be warned that the vaccine is not protective of previous infection and does not "cure" a chronic carrier. It should be stressed that the vaccine does not make high-risk behavior any safer; they remain at high risk for acquiring all other STDs unless they use appropriate preventive measures (118).

Although the importance of completing the three-dose series to assure (up to 99%) protective immunity should be stressed, partial completion of the vaccination series is not completely ineffective; a

**Table 1.** Recommended Doses of Currently Licensed Hepatitis B Vaccines (rev. 1995)*

| Patient Group | Recombivax HB Dose: μg | (mL) | Engerix-B Dose: μg | (mL) |
|---|---|---|---|---|
| Infants of HbsAg-negative mothers and children <11 y | 2.5 | (0.5)[a] | 10 | (0.5) |
| Infants of HbsAg-positive mothers | 5.0 | (0.5)[b] | 10 | (0.5) |
| (HBIG [0.5 mL] should also be given) | | (1.0)[a] | | |
| Children and adolescents 11-19 y | 5.0 | (0.5)[b] | 10 | (0.5) |
| Adults 20 y or older | 10.0 | (1.0)[b] | 20 | (1.0) |
| Dialysis patients and other immunosuppressed adults | 40.0 | (1.0)[c] | 40 | (2.0)[d] |

[a] Pediatric formulation.
[b] Adult formulation.
[c] Special formulation for dialysis patients.
[d] Two 1.0 mL doses administered at one site in a 4-dose schedule at 0,1,2 and 6-12 months.

* Committee on Infectious Diseases, American Academy of Pediatrics, Hepatitis B. In: Peter G, Halsey NA, Marcuse EK, et al, eds., Redbook 1994: Report of the Committee on Infectious Diseases. 1994; 224-238.

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study showed that 81% of healthy adolescents achieved protective antibody levels after only two doses of the vaccine (108).

Postvaccination screening for a serologic response is not necessary after routine vaccination of infants, children, or adolescents (19). If a protective antibody response develops after vaccination, vaccine recipients are virtually 100% protected against clinical illness (19). Booster doses of the vaccine are not currently recommended (19); long-term studies show that immunologic memory remains intact for at least 9 years (119) and confers protection against HBV even though antibody titers may fall below detectable levels (120,121).

### *Cost*

The hepatitis B vaccine is the only vaccine for an STD (122) and is considered to be the first effective anticancer vaccine (99,123), because of the strong association between HBV infection and primary hepatocellular carcinoma (4). Yet, cost and unfounded fear of HIV infection have limited its widespread acceptance (122). Fears concerning the earlier plasma-derived vaccine and the transmission of AIDS have been unfounded (40,124) and are nullified, as plasma-derived vaccines are no longer produced in the United States (20). Vaccine prices remain high, however. In the United States, the three-injection course costs $150–200 for an adult, although the recent lowering of dosage recommendations for adolescents receiving Engerix-B will lower the price of the series. Licensure of new vaccines should decrease the cost (122) of vaccine, and if a universal vaccination program for adolescents were to be implemented, a substantial reduction in the price of the vaccine could result from the high-volume sales it would generate (125). Because cost is a major factor in the cost-effectiveness of any universal hepatitis B immunization program (123), efforts should be made to investigate cooperation between pharmaceutical companies and federal health organizations concerning pricing and volume.

### *A Model for Future Vaccination Efforts*

Vaccinating adolescents and adults is substantially more expensive than vaccinating infants, because of their larger dose requirements and the higher implementation costs of delivering vaccine to target populations (19). Although it is cost-effective, start-up costs of any universal immunization program will be large (99).

Although vaccinating all children nearing, or in, adolescence should be a priority of the health care provider, this may not be economically feasible at this time. Several models have been proposed most efficiently and effectively to vaccinate the unimmunized cohort when resources allow. The AAP recommends vaccinating children at an earlier age than 11 years (22), because better immune responses are seen in younger persons (126) and younger children require lower doses (22). In studies using three 5 μg doses (half the adult dose) for children under 12 years old, over 99% developed protective antibodies (14). Moreover, because age at acute infection is inversely related to the likelihood of chronic illness, immunizing children as young as possible will have the greatest effect on minimizing the chronic carrier population.

If hepatitis B vaccination is not readily accessible through the adolescent's usual source of health care, then vaccination could be done in schools either by the school nurse or during schoolwide vaccination drives. The first year could involve mass vaccination of all children 10 years of age and older. Universal vaccination of adolescents will result in a more rapid reduction of HBV transmission and infection in this group most at risk of acquiring HBV infection (20). When resources do not permit vaccination of multiple-age cohorts of adolescents, an alternative approach is continuous vaccination of students in a single grade or age cohort (98). Subsequent years efforts would therefore only need to focus on vaccinating each new 10-year-old cohort. Bloom et al. suggest proof of HBV immunization be required for entrance into middle or junior high school (123). Some colleges (99) are contemplating making immunization an admission requirement. Beginning in 1996, the Commonwealth of Massachusetts will require children entering kindergarten to be immunized against hepatitis B.

Unlike most preventive health care programs, a universal infant hepatitis B vaccination program dictates a several-decade perspective (123). Incurring costs of infant vaccination today results in savings in the future by preventing infection in 20 years, and chronic liver disease, hepatoma, and death in 60 years (125). A universal adolescent vaccination program would result in the most immediate health benefits and acceleration toward the eradication of HBV in the United States.

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## References


1. Maynard JE, Kane MA, Alter MJ, et al. Control of hepatitis B by immunization: Global perspectives. In: Zuckerman AJ, ed., Viral Hepatitis and Liver Disease. New York: Alan R. Liss, 1988:967–969.
2. Szmuness W, Harley E, Ikram H, et al. Sociodemographic aspects of the epidemiology of hepatitis B. In: Vyas GN, Cohen SN, Schmid R, eds., Viral Hepatitis. Philadelphia: Franklin Institute Press, 1978:17–21.
3. Maynard JE. Hepatitis B: Global importance and need for control. Vaccine 1990;8(Suppl):18s–20s.
4. Beasley PR. Hepatitis B virus: The major etiology of hepatocellular carcinoma. Cancer 1988;61:1942–1956.
5. Beasley PR, Hwang LY, Lin CC. Hepatocellular carcinoma and the hepatitis B virus. Lancet 1981;ii:1129–1133.
6. Sung JL. Asian Regional Study Group. Hepatitis virus eradication strategy for Asia. Vaccine 1990;8(Suppl):s96–s99.
7. Stevens CE, Beasley RP, Tsui J, et al. Vertical transmission of hepatitis B antigen in Taiwan. N Engl J Med 1975;292:771–774.
8. Tong MJ. Hepatitis B vaccination of neonates and children. Am J Med 1989;87(Suppl 3A):33S–35S.
9. McQuillan GM, Townsend TR, Fields HA, et al. Seroepidemiology of hepatitis B in the United States: 1976 to 1980. Am J Med 1989;87:5S–10S.
10. Centers for Disease Control. Hepatitis Surveillance Report No. 52. Atlanta:CDC, 1989.
11. Alter MJ, Hadler SC, Margolis HS. The changing epidemiology of hepatitis B in the United States: Need for alternative vaccination strategies. JAMA 1990;263:1218–1222.
12. Margolis HS, Alter MJ, Hadler SC. Hepatitis B: Evolving epidemiology and implications for control. Semin Liver Dis 1991;11:84–92.
13. Centers for Disease Control. Protection against viral hepatitis: Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1990;39(RR-2):1–26.
14. Centers for Disease Control. Update on hepatitis B prevention. MMWR 1987;36:353–366.
15. Hoofnagle JH. Toward universal vaccination against hepatitis B virus. N Engl J Med 1989;321:1333–1334.
16. Engelhardt JA, Halsey NA, Eddins DL, et al. Measles mortality in the United States, 1971–1975. Am J Pub Health 1980;70:1166–1169.
17. Cochi SL, Ward JI. *Haemophilis influenzae* type b. In: Evans AS, Brachman PS, eds., Bacterial Infections of Humans: Epidemiology and Control. New York: Plenum, 1991:271–332.
18. Tolsma DD, Bryan JA. The economic impact of viral hepatitis in the United States. Pub Health Rep 1976;91:349–353.
19. Centers for Disease Control. Hepatitis B virus: A comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination: recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1991;40(RR-13):1–25.
20. American Academy of Pediatrics. Universal hepatitis B immunization. Pediatrics 1992;89:795–800.
21. Elster AB, Kuznets NJ. AMA Guidelines for adolescent preventive services (GAPS): Recommendations and rationale. Chicago: AMA, 1994:167–171.
22. Committee on Infectious Diseases, American Academy of Pediatrics. Hepatitis B. In: Peter G, Halsey NA, Marcuse EK, et al. eds., Redbook 1994: Report of the Committee on Infectious Diseases. 1994;224–238.
23. Villarejos VM, Visona KA, Gutierrez A, et al. Role of saliva, urine and feces in the transmission of type B hepatitis. N Engl J Med 1974;291:1375–1378.
24. Heathcote J, Cameron CH, Dane DS. Hepatitis-B antigen in saliva and semen. Lancet 1974;i:71–73.
25. Darani M, Gerber M. Hepatitis B antigen in vaginal secretions. Lancet 1974;ii:1008.
26. Heathcote J, Sherlock S. Spread of acute type hepatitis in London. Lancet 1973;i:1468–1473.
27. Jeffries DJ, James WH, Jefferis FJG, et al. Australia (hepatitis associated) antigen in patients attending a venereal disease clinic. BMJ 1973;2:455–456.
28. Fulford KWM, Dane DS. Australia antigen and antibody among patients attending a clinic for sexually transmitted disease. Lancet 1973;i:1470–1473.
29. Shapiro CN. Transmission of hepatitis viruses (edit). Ann Intern Med 1994;120:82–84.
30. Shapiro CN, McCaig LF, Genscheimer KF, et al. Hepatitis B transmission between children in day care. Pediatr Infect Dis J 1989;8:870–875.
31. Alter MJ, Mares A, Hadler SC, et al. The effect of underreporting on the apparent incidence and epidemiology of acute viral hepatitis. Am J Epidemiol 1987;125:133–139.
32. Szmuness W, Prince AM, Brotman B, et al. Hepatitis B antigen and antibody in blood donors: An epidemiologic study. J Infect Dis 1973;127:17–25.
33. Koff RS. Hepatitis B today: Clinical and diagnostic overview. Pediatr Infect Dis J 1993;12:428–432.
34. Centers for Disease Control. Changing patterns of groups at high risk for hepatitis B in the United States. MMWR 1988;37:429–437.
35. Schatz G, Hader S, McCarthy J, et al. Outreach to needle users and sexual contacts: A multi-year community-wide hepatitis B/delta hepatitis control program in Worcester, Massachusetts. In: Coursaget P, Tong MJ, eds., Progress in Hepatitis B Immunization. London: John Libbey, 1990.
36. U.S. Preventive Services Task Force. Counseling to prevent HIV infection and other sexually transmitted diseases. AFP 1990;41:1179–1187.
37. Lewis CE, Freeman HE. The sexual history-taking and counseling practices of primary care physicians. Western J Med 1987;147:165–167.
38. United States Department of Health and Human Services Public Health Service. Hepatitis Surveillance Report No 50., 1986.
39. Alter MJ, Coleman PJ, Alexander WJ, et al. Importance of heterosexual activity in the transmission of hepatitis B and non-A, non-B hepatitis. JAMA 1990;262:1201–1205.
40. Centers for Disease Control. Safety of therapeutic immune globulin preparations with respect to transmission of human T-lymphotrophic virus type III/lymphadenopathy-associated virus infection. MMWR 1986;35:231–233.
41. Centers for Disease Control. Self-reported behavioral change among gay and bisexual men—San Francisco. MMWR 1985; 34:613–615.
42. Centers for Disease Control. Self-reported change in sexual behaviors among homosexual and bisexual men from the San Francisco city clinic cohort. MMWR 1987;36:187–189.
43. Winkelstein W, Wiley JA, Padian NS, et al. The San Francisco men's health study: continued decline in HIV seroconversion

rates among homosexual/bisexual men. Am J Public Health 1988;78:1472–1474.

44. Becker MH, Joseph JG. AIDS and behavioral change to reduce risk: A review. Am J Public Health 1988;78:394–410.
45. Goilav C, Piot P. Vaccination against hepatitis B in homosexual men: A review. Am J Med 1989;87(Suppl 3A):21S–25S.
46. Winkelstein W, Samuel M, Padian NS, et al. The San Francisco Men's health study: III. Reduction in human immunodeficiency virus transmission among homosexual/bisexual men, 1982–1986. Am J Public Health 1987;76:685–689.
47. Martin J. The impact of AIDS on gay male sexual behavior patterns in New York City. Am J Public Health 1987;77:578–581.
48. McKusick L, Wiley JA, Coates TJ, et al. Reported changes in the sexual behavior of men at risk for AIDS, San Francisco, 1982–84—the AIDS Behavioral Research Project. Pub Health Rep 1985;100:622–629.
49. Stall R, Barrett D, Bye L, et al. A comparison of younger and older gay men's HIV risk-taking behaviors: The Communication Technologies 1989 cross-sectional survey. J Acquir Immune Defic Syndr 1992;5:682–687.
50. Hays RB, Kegeles SM, Coates TJ. High HIV risk-taking among young gay men. AIDS 1990;4:901–907.
51. Lemp GF, Hirozawa AM, Givertz D, et al. Seroprevalence of HIV and risk behaviors among young homosexual and bisexual men. JAMA 1994;272:449–454.
52. Ekstrand ML, Coates TJ. Maintenance of safer sexual behaviors and predictors of risky sex: The San Francisco Men's Health Study. Am J Pub Health 1990;80:973–977.
53. Kelly J, St. Lawrence J, Brasfield T. Predictors of vulnerability to AIDS risk behavior relapse. J Consult Clin Psychol 1991; 59:163–166.
54. Valdiserri RO, Lyter LD, Leviton CM, et al. Variables influencing condom use in a cohort of gay and bisexual men. Am J Pub Health 1988;78:801–805.
55. Sylvestre AJ, Kingsley LA, Wehman P, et al. Changes in HIV rates and sexual behavior among homosexual men 1984 to 1988/92. Am J Pub Health 1993;83:578–580.
56. Keller SE, Bartlett JA, Schleifer SJ, et al. HIV-relevant sexual behavior among a healthy inner-city heterosexual adolescent population in an endemic area of HIV. J Adolesc Health 1991;12:44–48.
57. Cates WJ. Teenagers and sexual risk taking: The best of times and the worst of times. J Adolesc Health 1991;12:84–94.
58. Kegeles SM, Adler NE, Irwin CE. Sexually active adolescents and condoms: Changes over one year in knowledge, attitudes and use. Am J Pub Health 1988;78:460–461.
59. Strunin L, Hingson R. Acquired immunodeficiency syndrome and adolescents: Knowledge beliefs, attitudes, and behaviors. Pediatrics 1987;91:350–355.
60. Landefeld CS, Chren MM, Shega J, et al. Students' sexual behavior, knowledge, and attitudes relating to the acquired immunodeficiency syndrome. J Gen Intern Med 1994;3:161–165.
61. Weisman CS, Nathtanson CA, Ensminger M, et al. AIDS knowledge, perceived risk and prevention among adolescent clients of a family planning clinic. Fam Plann Pers 1989;21: 213–217.
62. Stanton B, Li X, Black M, et al. Sexual practices and intentions among preadolescent and early adolescent low-income urban African-Americans. Pediatrics 1994;93:966–973.
63. Sonenstein FL, Pleck JH, Ku LC. Sexual activity, condom use and AIDS awareness among adolescent males. Fam Plann Perspect 1989;21:152–158.
64. Higgins DL, Galavotti C, O'Reilly KR, et al. Evidence for the effects of HIV antibody counseling and testing on risk behaviors. JAMA 1991;266:2419–2429.
65. Roscoe B, Kruger TL. AIDS: late adolescents' knowledge and its influence on sexual behavior. Adolescence 1990;25:39–48.
66. Overby KJ, Lo B, Litt IF. Knowledge and concerns about acquired immunodeficiency syndrome and their relationship to behavior among adolescents with hemophilia. Pediatrics 1989;83:204–210.
67. DeBuono BA, Zinner SH, Daamen M, et al. Sexual behavior of college women in 1975, 1986 and 1989. N Engl J Med 1990;322:821–825.
68. Kaplan EH, Heimer R. HIV prevention among intravenous drug users: Model-based estimates of New Hampshire's legal needle exchange. J Acquir Immun Syndr 1992;30:163–169.
69. O'Keefe E, Kaplan EH, Khoshnood K. Analysis of New Hampshire's needle exchange program: Preliminary report. In: New Hampshire: City Health Report, 1991:1–46.
70. Centers for Disease Control. Premarital sexual experience among adolescent women—United States, 1970–1988. MMWR 1991;39:929–932.
71. Alter MJ, Ahtone J, Weisfuse I, et al. Hepatitis B transmission between heterosexuals. JAMA 1986;256:1307–1310.
72. Rosenblum LS, Hadler SC, Castro KG, et al. Heterosexual transmission of hepatitis B in Belle Glade, Florida. J Infect Dis 1990;161:407–411.
73. Aral SO, Holmes KK. Epidemiology of sexual behavior and sexually transmitted diseases. In: Holmes KK, et al., eds., Sexually Transmitted Diseases. New York: McGraw-Hall, 1990:19–36.
74. Schydlower M, Schafer MA. Adolescent Medicine: State of the Art Reviews: AIDS and Other Sexually Transmitted Diseases. 1990:416.
75. O'Reilly KR, Aral SO. Adolescence and sexual behavior: trends and implications for STD. J Adolesc Health Care 1985;6:262–270.
76. Kann L, Warren W, Collins JL, et al. Results from the national school-based 1991 youth risk behavior survey and progress towards achieving related health objectives for the nation. Pub Health Rep 1993;108(Suppl 1):47–55.
77. Center for Disease Control. Sexual behavior among high school students—United States, 1990. MMWR 1991;40:885–888.
78. Center for Disease Control. Health-risk behaviors among persons aged 12–21 years—United States, 1992. MMWR 1994;43:231–235.
79. Rosenfeld WD. Sexually transmitted diseases in adolescents: Update 1991. Pediatr Ann 1991;20:6:303–312.
80. Hayes CD. Risking the Future: Adolescent Sexuality, Pregnancy and Childbearing. Washington, DC: National Academy Press, 1987.
81. Kibrick S. The adolescent and education. In: Schinazi R, Nahmias A, eds. AIDS in Children, Adolescents and Heterosexual Adults: An Interdisciplinary Approach to Prevention. New York: Elsevier, 1988:323–324.
82. Igra VI, Millstein SG. Current status and approaches to improving preventive services for adolescents. JAMA 1993; 269:1408–1412.
83. Donovan P. Testing positive: sexually transmitted disease and the public health response. New York. Alan Guttmacher Institute, 1993.
84. Kipke M, Futterman D, Hein K. HIV infection and AIDS during adolescence. Med Clin N Amer 1990;74:1149–1167.

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85. Aral S, Schaffer JE, Mosher WD, et al. Gonorrhea rates: What denominator is most appropriate? Am J Pub Health 1988;78: 702–703.
86. Bell TA, Hein K. Adolescents and sexually transmitted diseases. In: Holmes K, et al., eds., Sexually Transmitted Diseases. New York: McGraw-Hill, 1984:73–84.
87. Cates WJ. The epidemiology and control of sexually transmitted diseases in adolescents. In: Schydlower M, Shafer MA, eds., AIDS and the Other Sexually Transmitted Diseases: Adolescent Medicine—State of the Art Reviews. Philadelphia: Hanley and Belfus, 1990:409–427.
88. Ku L, Sonenstein FL, Pleck JH. Young men's risk behaviors for HIV infection and sexually transmitted diseases, 1988 through 1991. Am J Pub Health 1993;83:1609–1615.
89. DesJarlais DC, Friedman SR, Hopkins W. Risk reduction for the acquired immunodeficiency syndrome among intravenous drug users. Ann Intern Med 1985;103:755–759.
90. Lewis DK, Watters JK. Sexual risk behavior among heterosexual intravenous drug user: Ethnic and gender variations. AIDS 1991;5:77–83.
91. Williams ML. Risk behaviors of IV drug using adolescents. In: National AIDS Demonstration Research Project. Rockville, MD: National Institute of Drug Abuse, 1990.
92. Elkind D. The Child's Reality: Three Developmental Themes. Hillsdale, NJ: Erlbaum, 1978.
93. Cvetkovich G, Grote B, Bjorseth A, et al. On the psychology of adolescent's use of contraceptives. J Sex Res 1975;11:256–270.
94. Hein K. AIDS in adolescence: Exploring the challenge. J Adolesc Health Care 1989;10:10S–35S.
95. Irwin CE, Millstein SG. Biopsychosocial correlates of risk-taking behaviors during adolescence. J Adolesc Health Care 1986;7:825–965.
96. Prothrow-Stith D. Excerpts from Address in the National Conference on "AIDS in Adolescents: Exploring the Challenge," New York City, 1988. J Adolesc Health Care 1989;10: 5S–7S.
97. Oppenheim GL, Bergman JJ, English EC. Failed appointments: A review. J Fam Pract 1979;8:789–796.
98. Centers for Disease Control. Hepatitis B vaccination of adolescents—California, Louisiana, and Oregon, 1992–1994. MMWR 1994;43:605–609.
99. Schaffner W, Gardner P, Gross PA. Hepatitis B immunization strategies: Expanding the target (edit). Ann Intern Med 1993;118:308–309.
100. Schiff GM, Sherwood JR, Zeldis JB, Krause DS. Comparative study of the immunogenicity and safety of two doses of recombinant hepatitis B vaccine in healthy adolescents. J Adolesc Health 1995;16:12–17.
101. Weisman CS, Plitcha S, Nathanson CA, et al. Consistency of condom use for disease prevention among adolescent users of oral contraceptives. Fam Plann Perspect 1991;23:71–74.
102. Brookman RR. Adolescent sexual behavior. In: Holmes KK, et al. eds., Sexually Transmitted Diseases. New York: McGraw-Hill, 1990.
103. Morrison DM. Adolescent contraceptive behavior: A review. Psychol Bull 1985;98:538–568.
104. Friedman IM, Litt IF. Promoting adolescents' compliance with therapeutic regimens. Pediatr Clin N Am 1986;33:955–973.
105. Jay S, Litt IF, DuRant MA. Compliance with therapeutic regimens (review). J Adolesc Health Care 1984;5:124–136.
106. Smith PB, Chacko MR, McGill L, et al. Sexually transmitted disease treatment and return for test of cure of adolescents in a family planning clinic. J Adolesc Health 1991;12:49–52.
107. Irwin CE, Millstein SG, Ellen JM. Appointment-keeping behavior in adolescents: Factors associated with follow-up appointment-keeping. Pediatrics 1993;92:20–23.
108. West DJ. Clinical experience with hepatitis B vaccines. Am J Infect Control 1989;17:172–180.
109. Cromer B, Chacko M, Phillips S. Increasing appointment compliance through telephone reminders: Does it ring true? Dev Behav Pediatrics 1987;8:133–135.
110. Chacko MR, Wells RD, Phillips SA. Test of cure for gonorrhea in teenagers: Who complies and does continuity of care help? J Adolesc Health Care 1987;8:261–265.
111. Kwan-Gett TS, Whitaker RC, Kemper KJ. A cost-effectiveness analysis of prevaccination testing for hepatitis B in adolescents and preadolescents. Arch Pediatr Adolesc Med 1994; 148:915–920.
112. Hertz P, Stamps PL. Appointment-keeping behavior reevaluated. Am J Pub Health 1977;67:1033–1036.
113. Becker MH, Drachman RH, Kirscht JP. Continuity of pediatrician: New support for an old Shibboleth. J Pediatr 1974;84: 599–605.
114. Litt IF, Cuskey WR. Satisfaction with health care: A predictor of adolescents' appointment keeping. J Adolesc Health Care 1984;5:196–200.
115. Haynes RB. Strategies for enhancing patient compliance. Drug Ther 1982:33–40.
116. Hall CB, Halsey NA. Control of hepatitis B: To be or not to be? (edit). Pediatrics 1992;90:274–277.
117. Dienstag JL, Stevens CE, Bhan AK, et al. Hepatitis B vaccine administered to chronic carriers of hepatitis B surface antigen. Ann Intern Med 1982;96:575–579.
118. Centers for Disease Control. Condoms for prevention of sexually transmitted diseases. MMWR 1988;37:133–137.
119. Hadler SC, Francis DP, Maynard JE, et al. Long-term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. N Engl J Med 1986;315:209–214.
120. Lo KJ, Lee SD, Tsai YT, et al. Long-term immunogenicity and efficacy of hepatitis B vaccine in infants born to Hbeag-positive Hbsag-carrier mothers. Hepatology 1988;8: 1647–1650.
121. Wainwright RB, McMahon BJ, Bulkow LR, et al. Duration of immunogenicity and efficacy of hepatitis B vaccine in a Yupik Eskimo population. JAMA 1989;261:2362–2366.
122. Public Health Service. Healthy People 2000: National health promotion and disease prevention objectives—full report, with commentary. Washington, DC: U.S. Department of Health and Human Services, Public Health Service, 1991; DHHS publication No. (PHS) 91–50212.
123. Bloom BS, Hillman AL, Fendrick M, et al. A reappraisal of hepatitis B virus vaccination strategies using cost-effectiveness analysis. Ann Intern Med 1993;118:298–306.
124. Francis DP, Feorino PM, McDougal S, et al. The safety of hepatitis B vaccine: Inactivation of the AIDS virus during routine vaccine manufacture. JAMA 1986;256:869–872.
125. Krahn MD, Detsky AS. Universal hepatitis B vaccination: The economics of prevention (edit). Can Med Assoc J 1992;146: 19–21.
126. Zajac BA, West DJ, McAleer WJ, et al. Overview of clinical studies with hepatitis B vaccine made by recombinant DNA. J Infection 1986;13(Suppl A):39–45.


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