**Rationale for Hepatitis B Immunization Strategies in the United States**

In the United States, hepatitis B virus (HBV) transmission occurs in all age groups and a comprehensive strategy is needed to provide widespread immunity and to effectively prevent HBV-related chronic liver disease.  Beginning in the late 1980s, the Advisory Committee on Immunization Practices to the U.S. Public Health Service developed a comprehensive strategy to eliminate HBV transmission in the United States (1).  This strategy includes 1) screening of all pregnant women for hepatitis B surface antigen (HBsAg) and providing postexposure immunoprophylaxis beginning at birth to infants of HBsAg-positive mothers; 2) routine infant vaccination; 3) catch-up vaccination of previously unvaccinated children and adolescents; and 4) vaccination of adults in high risk groups.  The following is an overview of the scientific basis for this immunization strategy, including hepatitis B disease burden, routes of HBV transmission, effectiveness of hepatitis B immunization, and safety of vaccination.

**Hepatitis B Disease Burden**
Hepatitis B is a serious liver disease that causes substantial morbidity and mortality in the United States.  In the two decades prior to the introduction of routine infant hepatitis B immunization in the United States in 1991, approximately 200,000-300,000 persons were infected with HBV annually, and the average lifetime risk of HBV infection was approximately 5% (2,3).  In addition, approximately 1.25 million persons remain chronically infected and about 4-5000 people die each year from HBV-related liver disease (4). Approximately 300 of these deaths are due to fulminant hepatitis, 3000 to 4000 to cirrhosis, and 600 to 1000 to primary hepatocellular carcinoma.  Annually, HBV-related liver disease is estimated to produce medical and work-loss costs of at least $700 million.  Cost-benefit analysis has shown that childhood hepatitis B immunization is cost-saving for society (5)

**Routes of HBV Transmission**
Hepatitis B virus is transmitted by either percutaneous or mucous membrane contact with infected blood or other body fluids (6).  The virus is found in highest concentrations in blood and serous exudates (as high as $10^{8-9}$ virions/mL); lower concentrations are found in various body secretions, including saliva, semen and vaginal fluid.  Transmission of HBV occurs in all age groups. The major routes of transmission in children are perinatal and  early childhood exposures.  The major routes of transmission among adolescents and adults are sexual contact and percutaneous exposures to blood or infectious body fluids (e.g., injection drug use).  HBV is not transmitted by air, food or water.

*Perinatal and early childhood HBV transmission*
Perinatal and early childhood HBV infections are usually not recognized because less than 1% of infants and <10% of children under 5 years of age have symptoms when first infected (7).  However, chronic infection develops in about 90% of children infected at birth, 30%-60% of children infected between 1 to 5 years of age and 2%-6% of older children and adults (8,9).  The risk of death from HBV-related liver cancer or cirrhosis is approximately 25% for persons who become chronically infected during early childhood (10,11).

Perinatal HBV transmission usually occurs at the time of birth.  In the United States, approximately 22,000 infants are born to HBV-infected pregnant women each year; without immunoprophylaxis, approximately 6,000 of these infants would develop chronic HBV infection (12).  These perinatally-acquired infections represented approximately 15%-20% of all chronic infections in the United States before perinatal hepatitis B prevention programs were implemented (5).

There has been a general misconception that young children in the United States do not become infected with HBV except through perinatal transmission from a HBsAg-positive mother. However, it is estimated that 16,000 children <10 years of age were infected with HBV, beyond the postnatal period, annually before integration of hepatitis B vaccine into the infant immunization schedule (13). Although these infections represented only 5%-10% of all HBV infections in the United States, approximately 18% of persons with chronic HBV infection acquired their infection postnatally during early childhood before implementation of perinatal hepatitis B immunization programs and routine infant hepatitis B immunization (5). In some populations, childhood transmission was more important than perinatal transmission as a cause of chronic HBV infection before hepatitis B immunization was widely implemented. For example, in studies conducted among US-born children of Southeast Asian refugees during the 1980s approximately 60% of chronic infections in young children were among children born to HBsAg-negative mothers (14,15). Thus, many of these childhood infections would not be prevented by programs that screen pregnant women for HBsAg and provide immunoprophylaxis to infants born to HBsAg-positive mothers.

Most early childhood HBV transmission occurs in households of persons with chronic infection, but transmission has also been recognized in child day care centers and in schools (16). The most probable mechanisms of early childhood transmission involve inapparent percutaneous or permucosal contact with infectious body fluids such as exudates from dermatologic lesions, breaks in the skin, or mucous membranes with blood or serous secretions (6). HBV may also spread because of contact with saliva through bites or other breaks in the skin, as a consequence of the premastication of food, and through contact with virus from inanimate objects such as shared towels or toothbrushes or reuse of needles. HBV remains infectious for at least seven days outside the body and can be found in titers of $10^{2-3}$ virions/mL on objects, even in the absence of visible blood (17,18).

*HBV transmission among adolescents and adults*
HBV is efficiently transmitted by sexual contact and by percutaneous exposures, and these exposures account for about 50% and 15%, respectively, of new infections among adults in the United States (19). The most common risk factors for sexual transmission among heterosexuals include multiple sexual partners (>1 partner in a 6 month period), history of a sexually transmitted disease, or sex with a known infected person. Men who have sex with men are also at high risk of sexually transmitted HBV transmission. The primary source of percutaneous exposures in the United States is injection of illicit drugs. In addition, HBV transmission from unsafe injections has been reported in medical settings.

**Effectiveness of Hepatitis B Immunization**
Hepatitis B vaccine induces protective levels of antibody to HBsAg (anti-HBs) in >95% of vaccinated infants and children, and in >90% of healthy young adults (16). Preexposure efficacy of hepatitis B vaccine in preventing acute and chronic HBV infection has been demonstrated in multiple controlled clinical trials (16). In addition, hepatitis B immunization is effective when administered after exposure to infants born to HBsAg-positive mothers and to persons with percutaneous exposures to infectious blood and body fluids (16).

The effectiveness of routine infant hepatitis B vaccination in significantly reducing or eliminating transmission of chronic HBV infection has been demonstrated in a variety of countries and settings. For example, in long-term follow-up studies among Alaskan Native children, the prevalence of chronic HBV infection declined from approximately 10% before routine infant hepatitis B vaccination was initiated in 1983 to 0% in 1993 (20). In addition, the proof of concept that a reduction in chronic HBV infection will lead to a reduction in cases of liver cancer has been

demonstrated (21,22). A number of cohort studies have shown that persons vaccinated as infants, children, or adults, with a 3-dose immunization series retain protection from HBV infection for as long as 15 years (16). Immunized persons remain protected from acute disease and chronic infection, even if they lose detectable anti-HBs, and booster doses of vaccine are not recommended. Thus, long-term protection following infant vaccination is expected to last for decades and ultimately protect against infections acquired in all age groups.

The implementation of routine infant immunization will eventually produce broad population-based immunity to HBV infection and prevent HBV transmission among all age groups. However, there continues to be a substantial disease burden from chronic infections acquired by older children, adolescents, and adults in the United States. Thus, vaccinating infants alone will not substantially lower the incidence of the disease for decades, and catch-up strategies targeted to unvaccinated persons in older age groups are needed to hasten the development of population-based immunity and to more rapidly decrease the incidence of acute hepatitis B. Target groups for catch-up immunization in the United States include previously unvaccinated children and adolescents, and adults in high risk groups.

**Safety of Hepatitis B Vaccine**
Numerous studies indicate that hepatitis B vaccines have an excellent safety profile. No serious adverse events were observed after hepatitis B vaccination in prelicensure clinical trials involving more than 200,000 recipients, including more than 50 studies of plasma-derived vaccines, and studies of 12 different recombinant vaccines (22). In addition, evaluations of large-scale infant hepatitis B immunization programs in Alaska, Taiwan, New Zealand, and the United States have observed no association between vaccination and the occurrence of serious adverse events (23,24,25,26,27).

Since hepatitis B vaccine became available in the United States in 1981, more than 40 million infants and children, and more than 30 million adolescents and adults have been vaccinated. During this time period the safety of the vaccine has been monitored through cases reported to the Vaccine Adverse Events Reporting System (VAERS), and reports of serious adverse events after hepatitis B vaccination have been rare. However, reporting of an adverse event in temporal relationship with receipt of any vaccine, including hepatitis B vaccine, does not differentiate between a true causal association and a coincidental temporal relationship. VAERS is a passive surveillance system that is designed to detect signal events that trigger more systematic investigations. These include studies to determine and compare rates of the suspect event in vaccinated and unvaccinated populations, studies that compare rates of the suspect event in the vaccinated population to rates in the general population, and studies that might explain the pathophysiologic basis for the suspect event. To date, a variety of serious adverse events that have been reported after hepatitis B vaccine have been investigated, and anaphylaxis has been the only one that has been judged by the Institute of Medicine Immunization Safety Review Committee or other expert panels to meet criteria for causality (23,28,29,30). Case reports of anaphylaxis following hepatitis B vaccination have been reported in the medical literature and a low rate of anaphylaxis has been observed in vaccine recipients based on reports to VAERS, with an estimated incidence of 1 case in 600,000 vaccine doses distributed (23). While none of the persons who have developed anaphylaxis died, anaphylaxis can be fatal and hepatitis B vaccine may cause a life-threatening hypersensitivity reaction in certain individuals and further vaccination is contraindicated in persons with a history of anaphylaxis after a previous dose of hepatitis B vaccine.

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