



CHAPTER

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*Hepatitis B
Immunization
in Childhood*

By Murray Krahn

Hepatitis B Immunization in Childhood

Adapted for the Canadian context by Murray Krahn, MD, MSc¹ from the report prepared for the U.S. Preventive Services Task Force²

Targeting high-risk groups for vaccination against hepatitis B infection has not had a major impact on the burden of disease. The incidence of both new hepatitis B infections and hepatitis B virus (HBV)-related deaths more than doubled between 1980 and 1989 in Canada. Poor compliance and difficulties in reaching high-risk groups prior to infection have hindered efforts to control disease transmission. Also, 30-40% of new cases come from groups with no identifiable risk factors. A consensus has emerged among HBV experts and advisory groups in the United States and Canada that universal immunization is the key to controlling HBV infection.

Burden of Suffering



Current vaccination strategies have not been effective in controlling HBV infection

2,815 new cases of hepatitis B were reported in Canada in 1992 (Laboratory Centre for Disease Control, Ottawa, unpublished data). The true incidence rate is 5 to 10 fold higher, because HBV is under reported, and most infection is subclinical. Between 1980 and 1988, death certificate data indicated that 223 deaths were caused by hepatitis B.<1>



Most new hepatitis B infections in North America occur in adults, but childhood infection accounts for a large proportion of adult chronic liver disease

Most HBV infections in North America occur in adults, presumably through sexual transmission, intravenous drug use, or contact with contaminated blood products. However, acute infection was also reported in 253 children aged 0-19 years of age, accounting for 9% of cases. Most were in adolescents, but 41 cases occurred in children under age 10. Incidence in this age group may be much higher, because HBV infections in infants and young children are rarely symptomatic.

Illness related to hepatitis B may be acute or chronic. Acute hepatitis B infection is most frequently asymptomatic, but may cause illness characterized by jaundice, systemic symptoms, and even liver failure or death. Acute infection may be followed by a chronic carrier state. HBV transmitted from HBsAg-positive mothers to their newborns results in HBV carriage in up to 90% of infants. Children infected before 5 years of age become chronic carriers in 25-50% of cases, compared to 5-10% of those infected as adults. Thus, although

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childhood infection is uncommon in North America, it accounts for a substantial proportion (40%, by one estimate^{<2>}) of HBV-related chronic hepatitis, cirrhosis, and hepatocellular carcinoma in adults. One third of all carriers with a life expectancy of greater than 30 years will die from complications of HBV-related liver disease.

Children who are at substantially increased risk of HBV infection include immigrants and refugees (or those born to such persons) from HBV endemic areas, native Canadians, children living in homes for the developmentally disabled, household contacts of HBV carriers, and infants born to HBsAg-positive mothers. Among North American-born children of Southeast Asian refugees, the prevalence of horizontally acquired HBV infection is nearly 10%.

Maneuver

All hepatitis B vaccines contain purified HBsAg, and induce production of antibodies (HBsAb) which provide protection against acute infection. Two vaccines are licensed in Canada, Recombivax HB (Merck Sharp and Dohme) and Engerix-B (Smith Kline Beecham). Both vaccines are derived from yeast strains that have been genetically manipulated, and contain HBsAg adsorbed on aluminum hydroxide along with trace amounts of yeast-derived proteins, lipids, polysaccharides, and DNA. Plasma-derived hepatitis B vaccines are no longer available in Canada.

Effectiveness of Prevention and Treatment

Health Benefit

Controlled trials^{<3,4>} and other studies have demonstrated that hepatitis B vaccine is 62-92% effective in preventing the development of the HBV chronic carrier state during the first 1-5 years of life when given to infants of HBsAg positive mothers soon after birth, again at 1 month, and then at either 6 months or 2 and 12 months of age. Efficacy in these studies has varied with dosage, vaccination interval, vaccine type, and hepatitis B e antigen status of the mother. The protective efficacy of vaccine when combined with hepatitis B immune globulin is higher (85-95%) than that of vaccine alone in these infants.

From controlled trials^{<5,6>} and time series conducted in populations where horizontal HBV transmission is common, universal vaccination of infants and children with a 3 or 4 dose regimen has been estimated to be >87% effective in preventing HBV infection and >80% effective in preventing chronic HBV carriage. Mass vaccination of children in New Zealand and infants in Taiwan has also led to substantial reductions in the prevalence of acute HBV events and carrier status in the unvaccinated population.



Controlled trials have shown that hepatitis B vaccine is effective in preventing new HBV infection and development of the carrier state

The long term efficacy of the vaccine is less certain. In Gambian children vaccinated before 5 years of age, and in Senegalese vaccinated as infants, protective efficacy against HBV events (as evidenced by HBsAg or anti-HB core antigen positivity) declined somewhat over time. However, protection against chronic carriage persisted at least 5-6 years in Gambian children and in the vaccinated infants of carrier mothers. Time series from populations with high endemicity have reported loss of protective antibody levels in 11-17% of children (ranging in age from 0-19 years) at 3-7 year follow-up although the risk of infection remained low. Booster vaccinations in children result in anamnestic responses suggesting that immunologic memory is maintained despite the decline in antibody levels. It is unclear whether these studies are applicable to the North American population, since malnutrition and infectious diseases may contribute to the loss of antibody and continued exposure to HBV may contribute to the maintenance of immunity. The exact role of such factors is undefined.

Many of the studies cited above used the plasma-derived hepatitis B vaccine that is no longer available in Canada. However, the recombinant vaccines currently in use induce similar antibody responses and similar short term efficacy in children and adults. Information on long-term efficacy of recombinant vaccines is not yet available. Continued experience will determine whether booster doses are necessary to maintain long-term protection.

Adverse Effects

Mild reactions to recombinant hepatitis B vaccine, including local soreness and induration, low grade fever, irritability and poor feeding, are reported by the parents of up to 13% of vaccinated children and 4-7% of vaccinated infants. No serious adverse effects have been reported in children, although an increased risk of Guillain-Barre syndrome associated with the plasma-derived vaccine has been suggested in adults. Neither the simultaneous administration of hepatitis B vaccine with diphtheria-tetanus-pertussis and oral polio vaccines, nor modest alterations in timing to integrate the hepatitis B vaccine with other childhood vaccines, appears to interfere substantially with the immunogenic effect of the vaccine. Immunologic response to hepatitis B vaccine increases with increasing intervals between the first and third doses, suggesting some advantage to postponing the third dose to coincide with later visits (e.g., at 12 to 18 months of age) for those at low risk. A reduced response of preterm infants to hepatitis B vaccine has been described, with one study reporting an improved seroconversion rate when the first dose was delayed a mean of 31 days in preterm infants.



No serious adverse reactions have been reported with the use of HBV vaccine in children, though local soreness, irritability, and fever are not uncommon

Costs

A recent cost effectiveness analysis^{<7>} compared a policy of maternal screening and vaccination of high risk neonates (those born to HBsAg positive mothers) with HBIG and hepatitis B vaccine to a combined policy of maternal screening and universal infant vaccination. The combined strategy resulted in a cost of approximately \$30,000 per additional year of life saved from a societal perspective, and \$60,000 per year of life saved from a third-party payer perspective (costs and life years discounted). Results of the analysis were sensitive to assumptions about the duration of vaccine efficacy, and cost of the vaccine.

Another study^{<8>} calculated that a universal vaccination strategy, when compared to no screening and no vaccination, resulted in a cost of approximately US\$40,000 per year of life saved. Universal vaccination of adolescents, compared to no vaccination, resulted in a cost of US\$100,000 per incremental life year (costs and life years discounted).

Recommendations of Others

The National Advisory Committee on Immunization (NACI) recommended that a universal immunization program during childhood be implemented, but stated that issues related to vaccine cost and optimal dose schedules should be resolved prior to implementation of a specific program.^{<9>} NACI also recommended the vaccination of high-risk children: children living in communities of high HBV endemicity in Canada (e.g. some native populations in Labrador and the Northwest Territories), children of immigrants from areas of high HBV endemicity aged < 7 years, residents of institutions for the developmentally challenged, hemophiliacs, dialysis patients, and household contacts of HBV carriers.

The Canadian Pediatric Society has advised that initial steps be taken to develop a universal hepatitis B vaccination program for infants, and consideration be given to a “catch up” program targeted at adolescents.^{<10>}

The American Academy of Pediatrics^{<11>} and the Advisory Committee on Immunization Practices^{<12>} advocate routine hepatitis B vaccination for all newborns, regardless of the HBsAg status of the mother. All groups recommend the addition of hepatitis B immune globulin (HBIG) to HBV vaccine for newborns of HBsAg-positive mothers, and vaccination of older children at high risk.

Conclusions and Recommendations

There is good evidence at this time to recommend that hepatitis B vaccination be incorporated in the childhood immunization schedule



HBV vaccine should be included in the childhood immunization schedule, but appropriate target populations and optimal dosage schedules have not yet been determined

as a component of the periodic health examination (A Recommendation). Universal childhood immunization should be implemented to control HBV infection, but the appropriate target population (adolescents or newborns) and the optimal dose schedules have not yet been determined. Infants born to HBsAg positive mothers should receive HBIG and hepatitis B vaccine at birth, as well as two additional vaccine doses at 1 and 6 months. Vaccination of high risk groups (described above) according to recommended schedules<13> should continue to receive high priority. Booster doses in immunocompetent individuals are not recommended.

Unanswered Questions (Research Agenda)

The duration of vaccine efficacy in North American populations remains uncertain and requires further study. The optimal strategy for universal vaccination is unclear.

Evidence

The literature was identified with a MEDLINE search for the years 1988 to January 1994 using the following MESH headings: Hepatitis B, prevention and control, Canada, vaccination, and immunization. This review was initiated by the Task Force in January 1994 and recommendations finalized in March 1994.

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Hepatitis B Immunization in Childhood

MANEUVER	EFFECTIVENESS	LEVEL OF EVIDENCE <REF>	RECOMMENDATION
Immunization with hepatitis B vaccine and hepatitis B immune globulin (HBIG) in infants born to hepatitis B surface antigen (HBsAg) positive mothers	Effective in preventing hepatitis B virus (HBV) infection and development of the carrier state in infants born to carrier mothers.	Randomized controlled trials<1,2> (I)	Good evidence to include in periodic health examination (A)
Immunization with hepatitis B vaccine in infants born to HBsAg negative mothers	Effective in preventing new HBV events and development of the carrier state in areas of high endemicity.	Randomized controlled trials<3,4> (I)	Good evidence to include in periodic health examination (A)
Immunization of high-risk* children and adolescents	Effective in preventing new HBV events and development of the carrier state in areas of high endemicity.	Randomized controlled trials<3,4> (I)	Good evidence to include in periodic health examination (A)*
Universal vaccination of children and adolescents	Effective in preventing new HBV events and development of the carrier state in areas of high endemicity	Randomized controlled trials<3,4> (I)	Good evidence to include in periodic health examination (A)

* High-risk groups include: residents of institutions for the developmentally challenged, hemophiliacs, hemodialysis patients, household contacts of HBV carriers, residents in HBV endemic communities, children <age 7 in immigrant families from HBV endemic areas, travellers to HBV endemic areas for >6 months.