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MMWR

Recommendations and Reports

February 09, 1990 / 39(RR-2);1-26

Protection Against Viral Hepatitis Recommendations of the Immunization Practices Advisory Committee (ACIP)

The following statement updates all previous recommendations on protection against viral hepatitis, including use of hepatitis B vaccine and hepatitis B immune globulin for prophylaxis of hepatitis B (MMWR 1985;34:313-24,329-35 and MMWR 1987,36:353-66), universal screening of pregnant women to prevent perinatal hepatitis B transmission (MMWR 1988;37:341-46,51), and use of immune globulin to prevent other types of viral hepatitis (MMWR 1985;34:313-24,329-35).

INTRODUCTION

The term "viral hepatitis" is commonly used for several clinically similar diseases that are etiologically and epidemiologically distinct (1). Two of these, hepatitis A (formerly called infectious hepatitis) and hepatitis B (formerly called serum hepatitis), have been recognized as separate entities since the early 1940s and can be diagnosed with specific serologic tests. A third category, currently known as non-A, non-B hepatitis, includes two epidemiologically distinct types of hepatitis: parenterally transmitted and enterically transmitted non-A, non-B hepatitis. Parenterally transmitted non-A, non-B hepatitis is associated with both posttransfusion and sporadic cases of acute hepatitis and may be caused by at least two different agents. Part of the genome for one of these agents has recently been cloned, and a candidate serologic assay for antibody to this virus (proposed as hepatitis C virus) has been developed (2,3). Enterically transmitted non-A, non-B hepatitis, which is spread by the fecal-oral route and is different from the types seen in the United States, has been reported in parts of Asia, Africa, and Mexico (4). Another distinct type of hepatitis, delta hepatitis, is an infection dependent on the hepatitis B virus. It may occur as a coinfection with acute hepatitis B infection or as superinfection of a hepatitis B carrier (5).

HEPATITIS SURVEILLANCE

Approximately 28,500 cases of hepatitis A, 23,200 cases of hepatitis B, 2,620 cases of non-A, non-B hepatitis, and 2,470 cases of hepatitis type unspecified were reported in 1988 in the United States. Most cases of each type occur among young adults. Since reporting from many localities is incomplete, the actual number of hepatitis cases occurring annually is thought to be several times the reported number.

IMMUNE GLOBULINS

Immune globulins are important tools for preventing infection and disease before or after exposure to hepatitis

viruses. Immune globulins used in medical practice are sterile solutions of antibodies (immunoglobulins) from human plasma. They are prepared by cold ethanol fractionation of large plasma pools and contain 10%-18% protein. In the United States, plasma is primarily obtained from paid donors. Only plasma shown to be free of hepatitis B surface antigen (HBsAg) and antibody to human immunodeficiency virus (HIV) is used to prepare immune globulins.

Immune globulin (IG) (formerly called immune serum globulin, ISG, or gamma globulin) produced in the United States contains antibodies against the hepatitis A virus (anti-HAV) and the HBsAg (anti-HBs). Hepatitis B immune globulin (HBIG) is an IG prepared from plasma containing high titers of anti-HBs.

There is no evidence that hepatitis B virus (HBV), HIV (the causative agent of acquired immunodeficiency syndrome (AIDS)), or other viruses have ever been transmitted by IG or HBIG commercially available in the United States (6). Since late April 1985, all plasma units for preparation of IGs have been screened for antibody to HIV, and reactive units are discarded. No instances of HIV infection or clinical illness have occurred that can be attributed to receiving IG or HBIG, including lots prepared before April 1985. Laboratory studies have shown that the margin of safety based on the removal of HIV infectivity by the fractionation process is extremely high (7). Some HBIG lots prepared before April 1985 have detectable HIV antibody. Shortly after being given HBIG, recipients have occasionally been noted to have low levels of passively acquired HIV antibody, but this reactivity does not persist (8).

Serious adverse effects from IGs administered as recommended have been rare. IGs prepared for intramuscular administration should be used for hepatitis prophylaxis. IGs prepared for intravenous administration to immunodeficient and other selected patients are not intended for hepatitis prophylaxis. IG and HBIG are not contraindicated for pregnant or lactating women.

HEPATITIS A

Hepatitis A is caused by the hepatitis A virus (HAV), a 27-nm ribonucleic acid (RNA) agent that is classified as a picornavirus. Patients with illness caused by HAV characteristically have abrupt onsets of symptoms including fever, malaise, anorexia, nausea, abdominal discomfort, dark urine, and jaundice. Severity is related to age. Among children, most infections are asymptomatic, and illness is usually not accompanied by jaundice. Most infected adults become symptomatically ill with jaundice. The case-fatality rate among reported cases is about 0.6%.

Hepatitis A is primarily transmitted by person-to-person contact, generally through fecal contamination and oral ingestion. Transmission is facilitated by poor personal hygiene, poor sanitation, and intimate (intrahousehold or sexual) contact. In recent years, cases of hepatitis A among intravenous drug users, most likely due to person-to-person contact, have been reported with increasing frequency (9). Common-source epidemics from contaminated food and water also occur. Sharing utensils or cigarettes or kissing is not believed to transmit the hepatitis A virus.

The incubation period of hepatitis A is 15-50 days (average 28). High concentrations of HAV (108 particles/g) are found in stool specimens from infected persons. Virus in the feces reaches its highest concentration late in the incubation period and early in the prodromal phase of illness, and it diminishes rapidly once jaundice appears. Greatest infectivity is during the 2-week period immediately before the onset of jaundice. Viremia probably occurs during the period that the virus is shed in feces. Virus has not been found in urine. A chronic carrier state with HAV in blood or feces has not been demonstrated. Transmission of HAV by blood transfusion has been reported but is uncommon (10).

The diagnosis of acute hepatitis A is confirmed by finding IgM anti-HAV in serum collected during the acute or early convalescent phase of the disease. IgG anti-HAV, which appears in the convalescent phase of the disease and remains detectable in serum thereafter, confers enduring protection against the disease. Commercial tests are available to detect IgM anti-HAV and total anti-HAV in serum.

Although the incidence of hepatitis A in the United States in the 1980s was lower than that in the 1970s, a 26%

increase in incidence was observed between 1983 and 1988. It is still a common infection among older children and young adults. In 1988, 50% of reported cases of hepatitis in this country were attributable to hepatitis A.

Recommendations for IG Prophylaxis for Hepatitis A

Numerous field studies conducted in the past 4 decades confirm that IG given before exposure or during the incubation period of hepatitis A is protective against clinical illness (11-13). Its prophylactic value is greatest (80%-90%) when given early in the incubation period and declines thereafter (13). Recent tests have shown slightly decreased titers of anti-HAV in current IG lots compared with lots tested 8 years previously; however, no differences in IG efficacy have been noted.

Preexposure Prophylaxis

The major group for whom preexposure prophylaxis is recommended is international travelers. The risk of hepatitis A for U.S. citizens traveling abroad varies with living conditions, length of stay, and the incidence of hepatitis A infection in areas visited (14-16). In general, travelers to developed areas of North America, western Europe, Japan, Australia, and New Zealand are at no greater risk of infection than they would be in the United States. For travelers to developing countries, risk of infection increases with duration of travel and is highest for those who live in or visit rural areas, trek in back country, or frequently eat or drink in settings of poor sanitation. Nevertheless, recent studies have shown that many cases of travel-related hepatitis A occur in travelers with "standard" tourist itineraries, accommodations, and food and beverage consumption behaviors (16 and CDC unpublished data). In developing countries, travelers should minimize their exposure to hepatitis A and other enteric diseases by avoiding potentially contaminated water or food. Travelers should avoid drinking water (or beverages with ice) of unknown purity and eating uncooked shellfish or uncooked fruits or vegetables that they did not prepare.

IG is recommended for all susceptible travelers to developing countries (17). IG is especially important for persons who will be living in or visiting rural areas, eating or drinking in settings of poor or uncertain sanitation, or who will have close contact with local persons (especially young children) in settings with poor sanitary conditions. Persons who plan to reside in developing areas for long periods should receive IG regularly.

For travelers, a single dose of IG of 0.02 ml/kg of body weight is recommended if travel is for less than 3 months. For prolonged travel or residence in developing countries, 0.06 ml/kg should be given every 5 months. For persons who require repeated IG prophylaxis, screening for total anti-HAV before travel is useful to define susceptibility and eliminate unnecessary doses of IG for those who are immune. IG produced in developing countries may not meet the standards for purity required in most developed countries. Persons needing repeat doses overseas should use products that meet U.S. license requirements.

Postexposure Prophylaxis

Hepatitis A cannot be reliably diagnosed on clinical presentation alone, and serologic confirmation of index patients is recommended before contacts are treated. Serologic screening of contacts for anti-HAV before they are given IG is not recommended because screening is more costly than IG and would delay its administration.

For postexposure IG prophylaxis, a single intramuscular dose of 0.02 ml/kg is recommended. IG should be given as soon as possible after last exposure; giving IG more than 2 weeks after exposure is not indicated.

Specific recommendations for IG prophylaxis for hepatitis A depend on the nature of the HAV exposure.

1. Close personal contact. IG is recommended for all household and sexual contacts of persons with hepatitis A.

2. Day-care centers. Day-care facilities attended by children in diapers can be important settings for HAV transmission (18-20). IG should be administered to all staff and attendees of day-care centers or homes if a) one or more children or employees are diagnosed as having hepatitis A, or b) cases are recognized in two

or more households of center attendees. When an outbreak (hepatitis cases in three or more families) occurs, IG should also be considered for members of households that have children (center attendees) in diapers. In centers not enrolling children in diapers, IG need only be given to classroom contacts of an index patient.

3. Schools. Contact at elementary and secondary schools is usually not an important means of transmitting hepatitis A. Routine administration of IG is not indicated for pupils and teachers in contact with a patient. However, when an epidemiologic investigation clearly shows the existence of a school- or classroom-centered outbreak, IG may be given to persons who have close contact with patients.

4. Institutions for custodial care. Living conditions in some institutions, such as prisons and facilities for the developmentally disabled, favor transmission of hepatitis A. When outbreaks occur, giving IG to residents and staff who have close contact with patients with hepatitis A may reduce the spread of disease. Depending on the epidemiologic circumstances, prophylaxis can be limited or can involve the entire institution.

5. Hospitals. Routine IG prophylaxis for hospital personnel is not indicated. Rather, sound hygienic practices should be emphasized. Staff education should point out the risk of exposure to hepatitis A and should emphasize precautions regarding direct contact with potentially infective materials (21).

   Outbreaks of hepatitis A occur occasionally among hospital staff, usually in association with an unsuspected index patient who is fecally incontinent. Large outbreaks have occurred from contact with infected infants in neonatal intensive care units (10). In outbreaks, prophylaxis of persons exposed to feces of infected patients may be indicated.

6. Offices and factories. Routine IG administration is not indicated under the usual office or factory conditions for persons exposed to a fellow worker with hepatitis A. Experience shows that casual contact in the work setting does not result in virus transmission.

7. Common-source exposure. IG use might be effective in preventing foodborne or waterborne hepatitis A if exposure is recognized in time. However, IG is not recommended for persons exposed to a common source of hepatitis infection after cases have begun to occur, since the 2-week period during which IG is effective will have been exceeded.

   If a food handler is diagnosed as having hepatitis A, common-source transmission is possible but uncommon. IG should be administered to other food handlers but is usually not recommended for patrons (22). However, IG administration to patrons may be considered if all of the following conditions exist: a) the infected person is directly involved in handling, without gloves, foods that will not be cooked before they are eaten, and b) the hygienic practices of the food handler are deficient or the food handler has had diarrhea, and c) patrons can be identified and treated within 2 weeks of exposure. Situations in which repeated exposures may have occurred, such as in institutional cafeterias, may warrant stronger consideration of IG use.

HEPATITIS B

Hepatitis B infection is caused by the hepatitis B virus (HBV), a 42-nm, double-shelled deoxyribonucleic acid (DNA) virus of the class hepadnaviridae. Several well-defined antigen-antibody systems are associated with HBV infection (Table_1). HBsAg is found on the surface of the virus and is also produced in excess amounts, circulating in blood as 22-nm spherical and tubular particles. HBsAg can be identified in serum 30-60 days after exposure to HBV and persists for variable periods. Anti-HBs develops after a resolved infection and is responsible for long-term immunity. Antibody to the core antigen (anti-HBc) develops in all HBV infections and persists indefinitely. IgM anti-HBc appears early in infection and persists for greater than or equal to 6 months. It is a reliable marker of acute or recent HBV infection. A third antigen, hepatitis B e antigen (HBeAg), may be detected in samples from persons with acute or chronic HBV infection. The presence of HBeAg correlates with viral replication and high infectivity. Antibody to HBeAg (anti-HBe) develops in most HBV infections and

correlates with the loss of replicating virus and with lower infectivity.

The incubation period of hepatitis B is long (45-160 days; average = 120), and the onset of acute disease is generally insidious. Clinical symptoms and signs include anorexia, malaise, nausea, vomiting, abdominal pain, and jaundice. Extrahepatic manifestations of disease -- such as skin rashes, arthralgias, and arthritis -- can also occur. The case-fatality rate for reported cases is approximately 1.4%.

A variable proportion of individuals infected with HBV will become chronically infected with the virus. The HBV carrier is central to the epidemiology of HBV transmission. A carrier is defined as a person who is either HBsAg-positive on at least two occasions (at least 6 months apart) or who is HBsAg-positive and IgM anti-HBc negative when a single serum specimen is tested. Although the degree of infectivity is best correlated with HBeAg-positivity, any person positive for HBsAg is potentially infectious. The likelihood of becoming chronically infected with HBV varies inversely with the age at which infection occurs. HBV transmitted from HBsAg-positive mothers to their newborns results in HBV carriage for up to 90% of infants. Between 25% and 50% of children infected before 5 years of age become carriers, whereas only 6%-10% of acutely infected adults become carriers.

Carriers and persons with acute infection have the highest concentrations of HBV in blood and serous fluids. A lower concentration is present in other body fluids, such as saliva and semen. Transmission occurs via percutaneous or permucosal routes, and infective blood or body fluids can be introduced at birth, through sexual contact, or by contaminated needles. Infection can also occur in settings of continuous close personal contact (such as in households or among children in institutions for the developmentally disabled), presumably via inapparent or unnoticed contact of infective secretions with skin lesions or mucosal surfaces. Transmission of infection by transfusion of blood or blood products is rare because of routine screening of blood for HBsAg and because of current donor selection procedures. Transmission of HBV from infected health-care workers to patients is uncommon but has been documented during types of invasive procedures (e.g., oral and gynecologic surgery) (23,24). HBsAg-positive health-care workers need not be restricted from patient contact unless they have been epidemiologically associated with HBV transmission. Rather, they should be educated about the potential mechanisms of HBV transmission. Adherence to aseptic techniques minimizes the risk of transmission. HBV is not transmitted via the fecal-oral route.

Worldwide, HBV infection is a major cause of acute and chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma. The frequency of HBV infection and patterns of transmission vary markedly in different parts of the world. In the United States, Western Europe, and Australia, it is a disease of low endemicity, with infection occurring primarily during adulthood and with only 0.2%-0.9% of the population being chronically infected. In contrast, HBV infection is highly endemic in China and Southeast Asia, most of Africa, most Pacific Islands, parts of the Middle East, and in the Amazon Basin. In these areas, most persons acquire infection at birth or during childhood, and 8%-15% of the population are chronically infected with HBV. In other parts of the world, HBV infection is moderately endemic, with 2%-7% of the population being HBV carriers. Prevention strategies for populations in which HBV infection is highly endemic are directed at vaccinating infants with hepatitis B vaccine, usually beginning at birth, to prevent both perinatal and childhood transmission of infection (25). Recommendations for hepatitis B prophylaxis in other areas should be designed to maximize the interruption of HBV transmission in accordance with local patterns of transmission. The recommendations that follow are intended for use in the United States.

Hepatitis B Virus Infection in the United States

Each year, an estimated 300,000 persons, primarily young adults, are infected with HBV. One-quarter become ill with jaundice, more than 10,000 patients require hospitalization, and an average of 250 die of fulminant disease. The United States currently contains an estimated pool of 750,000-1,000,000 infectious carriers. Approximately 25% of carriers develop chronic active hepatitis, which often progresses to cirrhosis. Furthermore, HBV carriers have a risk of developing primary liver cancer that is 12-300 times higher than that of other persons. An estimated 4,000 persons die each year from hepatitis B-related cirrhosis, and more than 800 die from hepatitis B-related liver cancer.

Serologic surveys demonstrate that, although HBV infection is uncommon among adults in the general population, it is highly prevalent in certain groups. Those at risk, based on the prevalence of serologic markers of infection, are described in Table_2. Persons born in areas of high HBV endemicity and their descendents remain at high risk of infection, as do certain populations in which HBV is highly endemic (Alaskan Natives and Pacific Islanders). Certain lifestyles (e.g., homosexual activity, intravenous drug abuse) result in early acquisition of HBV infection and high rates of infection. Persons who have heterosexual activity with multiple partners are at significant risk of infection. Inmates of prisons have a high prevalence of HBV markers, usually because of parenteral drug abuse before or during imprisonment. Patients in custodial institutions for the developmentally disabled are also at increased risk of having HBV infection. Household contacts and sexual partners of HBV carriers are at increased risk, as are hemodialysis patients and recipients of certain plasma-derived products that have not been inactivated (e.g., anti-hemophilic factor).

Those at occupational risk of HBV infection include medical and dental workers, related laboratory and support personnel, and public service employees who have contact with blood, as well as staff in institutions or classrooms for the mentally retarded.

Hepatitis B Prevention Strategies in the United States

The incidence of reported acute hepatitis B cases increased steadily over the past decade and reached a peak in 1985 (11.50 cases/105/year), despite the introduction of hepatitis B vaccine 3 years previously. Incidence decreased modestly (18%) by 1988, but still remains higher than a decade ago. This minimal impact of hepatitis B vaccine on disease incidence is attributable to several factors. The sources of infection for most cases include intravenous drug abuse (28%), heterosexual contact with infected persons or multiple partners (22%), and homosexual activity (9%). In addition, 30% of patients with Hepatitis B deny any of the recognized risk factors for infection.

The present strategy for hepatitis B prevention is to vaccinate those individuals at high risk of infection. Most persons receiving vaccine as a result of this strategy have been persons at risk of acquiring HBV infection through occupational exposure, a group that accounts for approximately 4% of cases. The major deterrents to vaccinating the other high-risk groups include their lack of knowledge about the risk of disease and its consequences, the lack of public-sector programs, the cost of vaccine, and the inability to access most of the high-risk populations.

For vaccine to have an impact on the incidence of hepatitis B, a comprehensive strategy must be developed that will provide hepatitis B vaccination to persons before they engage in behaviors or occupations that place them at risk of infection. Universal HBsAg screening of pregnant women was recently recommended to prevent perinatal HBV transmission. The previous recommendations for selective screening failed to identify most HBsAg-positive pregnant women (27). As an alternative to high-risk-group vaccination, universal vaccination of infants and adolescents needs to be examined as a possible strategy to control the transmission of disease.

Hepatitis B Prophylaxis

Two types of products are available for prophylaxis against hepatitis B. Hepatitis B vaccines, first licensed in 1981, provide active immunization against HBV infection, and their use is recommended for both preexposure and postexposure prophylaxis. HBIG provides temporary, passive protection and is indicated only in certain postexposure settings.

HBIG

HBIG is prepared from plasma preselected to contain a high titer of anti-HBs. In the United States, HBIG has an anti-HBs titer of greater than 100,000 by radioimmunoassay (RIA). Human plasma from which HBIG is prepared is screened for antibodies to HIV; in addition, the Cohn fractionation process used to prepare this product inactivates and eliminates HIV from the final product. There is no evidence that the causative agent of AIDS (HIV) has been transmitted by HBIG (6).

Hepatitis B Vaccine

Two types of hepatitis B vaccines are currently licensed in the United States. Plasma-derived vaccine consists of a suspension of inactivated, alum-adsorbed, 22-nm, HBsAg particles that have been purified from human plasma by a combination of biophysical (ultracentrifugation) and biochemical procedures. Inactivation is a threefold process using 8M urea, pepsin at pH 2, and 1:4,000 formalin. These treatment steps have been shown to inactivate representatives of all classes of viruses found in human blood, including HIV (28). Plasma-derived vaccine is no longer being produced in the United States, and use is now limited to hemodialysis patients, other immunocompromised hosts, and persons with known allergy to yeast.

Currently licensed recombinant hepatitis B vaccines are produced by Saccharomyces cerevisiae (common baker's yeast), into which a plasmid containing the gene for the HBsAg has been inserted. Purified HBsAg is obtained by lysing the yeast cells and separating HBsAg from yeast components by biochemical and biophysical techniques. These vaccines contain more than 95% HBsAg protein. Yeast-derived protein constitutes no more than 5% of the final product.

Hepatitis B vaccines are packaged to contain 10-40 ug HBsAg protein/ml and are adsorbed with aluminum hydroxide (0.5 mg/ml). Thimerosal (1:20,000 concentration) is added as a preservative.

The recommended series of three intramuscular doses of hepatitis B vaccine induces an adequate antibody response * in greater than 90% of healthy adults and in greater than 95%of infants, children, and adolescents from birth through 19 years of age (29-31). The deltoid (arm) is the recommended site for hepatitis B vaccination of adults and children; immunogenicity of vaccine for adults is substantially lower when injections are given in the buttock (32). Larger vaccine doses (two to four times normal adult dose) or an increased number of doses (four doses) are required to induce protective antibody in a high proportion of hemodialysis patients and may also be necessary for other immunocompromised persons (such as those on immunosuppressive drugs or with HIV infection) (33,34).

Field trials of the vaccines licensed in the United States have shown 80%-95% efficacy in preventing infection or clinical hepatitis among susceptible persons (31,35). Protection against illness is virtually complete for persons who develop an adequate antibody response after vaccination. The duration of protection and need for booster doses are not yet fully defined. Between 30% and 50% of persons who develop adequate antibody after three doses of vaccine will lose detectable antibody within 7 years, but protection against viremic infection and clinical disease appears to persist (36-38). Immunogenicity and efficacy of the licensed vaccines for hemodialysis patients are much lower than in normal adults. Protection in this group may last only as long as adequate antibody levels persist (33).

Vaccine Usage

Primary vaccination comprises three intramuscular doses of vaccine, with the second and third doses given 1 and 6 months, respectively, after the first. Adults and older children should be given a full 1.0 ml divided by ose, while children less than 11 years of age should usually receive half (0.5 ml) this dose. See Table_3 for complete information on age-specific dosages of currently available vaccines. An alternative schedule of four doses of vaccine given at 0, 1, 2, and 12 months has been approved for one vaccine for postexposure prophylaxis or for more rapid induction of immunity. However, there is no clear evidence that this regimen provides greater protection than the standard three-dose series. Hepatitis B vaccine should be given only in the deltoid muscle for adults and children or in the anterolateral thigh muscle for infants and neonates.

For patients undergoing hemodialysis and for other immunosuppressed patients, higher vaccine doses or increased numbers of doses are required. A special formulation of one vaccine is now available for such persons (Table_3). Persons with HIV infection have an impaired response to hepatitis B vaccine. The immunogenicity of higher doses of vaccine is unknown for this group, and firm recommendations on dosage cannot be made at this time (34).

Vaccine doses administered at longer intervals provide equally satisfactory protection, but optimal protection is

not conferred until after the third dose. If the vaccine series is interrupted after the first dose, the second and third doses should be given separated by an interval of 3-5 months. Persons who are late for the third dose should be given this dose when convenient. Postvaccination testing is not considered necessary in either situation.

In one study, the response to vaccination by the standard schedule using one or two doses of one vaccine, followed by the remaining doses of a different vaccine, was comparable to the response to vaccination with a single vaccine. Moreover, because the immunogenicities of the available vaccines are similar, it is likely that responses in such situations will be comparable to those induced by any of the vaccines alone.

The immunogenicity of a series of three low doses (0.1 standard dose) of plasma-derived hepatitis B vaccine administered by the intradermal route has been assessed in several studies. The largest studies of adults show lower rates of developing adequate antibody (80%-90%) and twofold to fourfold lower antibody titers than with intramuscular vaccination with recommended doses (39 and CDC unpublished data). Data on immunogenicity of low doses of recombinant vaccines given intradermally are limited. At this time, intradermal vaccination of adults using low doses of vaccine should be done only under research protocol, with appropriate informed consent and with postvaccination testing to identify persons with inadequate response who would be eligible for revaccination. Intradermal vaccination is not recommended for infants or children.

All hepatitis B vaccines are inactivated (noninfective) products, and there is no evidence of interference with other simultaneously administered vaccines.

Data are not available on the safety of hepatitis B vaccines for the developing fetus. Because the vaccines contain only noninfectious HBsAg particles, there should be no risk to the fetus. In contrast, HBV infection of a pregnant woman may result in severe disease for the mother and chronic infection of the newborn. Therefore, pregnancy or lactation should not be considered a contraindication to the use of this vaccine for persons who are otherwise eligible.

Vaccine storage and shipment

Vaccine should be shipped and stored at 2 C-8 C but not frozen. Freezing destroys the potency of the vaccine.

Side effects and adverse reactions

The most common side effect observed following vaccination with each of the available vaccines has been soreness at the injection site. Postvaccination surveillance for 3 years after licensure of the plasma-derived vaccine showed an association of borderline significance between Guillain-Barre syndrome and receipt of the first vaccine dose (40). The rate of this occurrence was very low (0.5/100,000 vaccinees) and was more than compensated by disease prevented by the vaccine even if Guillain-Barre syndrome is a true side effect. Such postvaccination surveillance information is not available for the recombinant hepatitis B vaccines. Early concerns about safety of plasma-derived vaccine have proven to be unfounded, particularly the concern that infectious agents such as HIV present in the donor plasma pools might contaminate the final product.

Effect of vaccination on carriers and immune persons

Hepatitis B vaccine produces neither therapeutic nor adverse effects for HBV carriers (41). Vaccination of individuals who possess antibodies against HBV from a previous infection is not necessary but will not cause adverse effects. Such individuals will have a postvaccination increase in their anti-HBs levels. Passively acquired antibody, whether acquired from HBIG or IG administration or from the transplacental route, will not interfere with active immunization (42).

Prevaccination serologic testing for susceptibility

The decision to test potential vaccine recipients for prior infection is primarily a cost-effectiveness issue and should be based on whether the costs of testing balance the costs of vaccine saved by not vaccinating individuals who have already been infected. Estimation of cost-effectiveness of testing depends on three variables: the cost

of vaccination, the cost of testing for susceptibility, and the expected prevalence of immune individuals in the group.

Testing in groups with the highest risk of HBV infection (HBV marker prevalence greater than 20%, Table_2) is usually cost-effective unless testing costs are extremely high. Cost-effectiveness of screening may be marginal for groups at intermediate risk. For groups with a low expected prevalence of HBV serologic markers, such as health professionals in their training years, prevaccination testing is not cost-effective.

For routine testing, only one antibody test is necessary (either anti-HBc or anti-HBs). Anti-HBc identifies all previously infected persons, both carriers and those who are not carriers, but does not differentiate members of the two groups. Anti-HBs identifies persons previously infected, except for carriers. Neither test has a particular advantage for groups expected to have carrier rates of less than 2%, such as health-care workers. Anti-HBc may be preferred to avoid unnecessary vaccination of carriers for groups with higher carrier rates. If RIA is used to test for anti-HBs, a minimum of 10 sample ratio units should be used to designate immunity (2.1 is the usual designation of a positive test). If EIA is used, the positive level recommended by manufacturers is appropriate.

Postvaccination testing for serologic response and revaccination of nonresponders

Hepatitis B vaccine, when given in the deltoid, produces protective antibody (anti-HBs) in greater than 90% of healthy persons. Testing for immunity after vaccination is not recommended routinely but is advised for persons whose subsequent management depends on knowing their immune status (such as dialysis patients and staff). Testing for immunity is also advised for persons for whom a suboptimal response may be anticipated, such as those who have received vaccine in the buttock, persons greater than or equal to 50 years of age, and persons known to have HIV infection. Postvaccination testing should also be considered for persons at occupational risk who may have needle-stick exposures necessitating postexposure prophylaxis. When necessary, postvaccination testing should be done between 1 and 6 months after completion of the vaccine series to provide definitive information on response to the vaccine.

Revaccination of persons who do not respond to the primary series (nonresponders) produces adequate antibody in 15%-25% after one additional dose and in 30%-50% after three additional doses when the primary vaccination has been given in the deltoid (36). For persons who did not respond to a primary vaccine series given in the buttock, data suggest that revaccination in the arm induces adequate antibody in greater than 75%. Revaccination with one or more additional doses should be considered for persons who fail to respond to vaccination in the deltoid and is recommended for those who have failed to respond to vaccination in the buttock.

Need for vaccine booster doses

Available data show that vaccine-induced antibody levels decline steadily with time and that up to 50% of adult vaccinees who respond adequately to vaccine may have low or undetectable antibody levels by 7 years after vaccination. Nevertheless, both adults and children with declining antibody levels are still protected against hepatitis B disease. Current data also suggest excellent protection against disease for 5 years after vaccination among infants born to hepatitis B-carrier mothers. For adults and children with normal immune status, booster doses are not routinely recommended within 7 years after vaccination, nor is routine serologic testing to assess antibody levels necessary for vaccine recipients during this period. For infants born to hepatitis B-carrier mothers, booster doses are not necessary within 5 years after vaccination. The possible need for booster doses after longer intervals will be assessed as additional information becomes available.

For hemodialysis patients, for whom vaccine-induced protection is less complete and may persist only as long as antibody levels remain above 10 mIU/ml, the need for booster doses should be assessed by annual antibody testing, and booster doses should be given when antibody levels decline to less than 10 mIU/ml.

Groups recommended for preexposure vaccination

Persons at substantial risk of HBV infection who are demonstrated or judged likely to be susceptible should be vaccinated. They include the following:

1. Persons with occupational risk. HBV infection is a major infectious occupational hazard for health-care and public-safety workers. The risk of acquiring HBV infection from occupational exposures is dependent on the frequency of percutaneous and permucosal exposures to blood or blood products. Any health-care or public-safety worker may be at risk for HBV exposure depending on the tasks that he or she performs. If those tasks involve contact with blood or blood-contaminated body fluids, such workers should be vaccinated. Vaccination should be considered for other workers depending on the nature of the task (43).

   Risks among health-care professionals vary during the training and working career of each individual but are often highest during the professional training period. For this reason, when possible, vaccination should be completed during training in schools of medicine, dentistry, nursing, laboratory technology, and other allied health professions before workers have their first contact with blood.

2. Clients and staff of institutions for the developmentally disabled. Susceptible clients in institutions for the developmentally disabled should be vaccinated. Staff who work closely with clients should also be vaccinated. The risk in institutional environments is associated not only with blood exposure but may also be consequent to bites and contact with skin lesions and other infective secretions. Susceptible clients and staff who live or work in smaller (group) residential settings with known HBV carriers should also receive hepatitis B vaccine. Clients discharged from residential institutions into community settings should be screened for HBsAg so that the community programs may take appropriate measures to prevent HBV transmission. These measures should include both environmental controls and appropriate use of vaccine.

   Staff of nonresidential day-care programs (e.g., schools, sheltered workshops for the developmentally disabled) attended by known HBV carriers have a risk of HBV infection comparable to that among health-care workers and therefore should be vaccinated (44). The risk of HBV infection for clients appears to be lower than the risk for staff. Vaccination of clients in day-care programs may be considered. Vaccination of classroom contacts is strongly encouraged if a classmate who is an HBV carrier behaves aggressively or has special medical problems that increase the risk of exposure to his/her blood or serous secretions.

3. Hemodialysis patients. Hepatitis B vaccination is recommended for susceptible hemodialysis patients. Although seroconversion rates and anti-HBs titers are lower than those for healthy persons, for those patients who do respond, hepatitis B vaccine will protect them from HBV infection and reduce the necessity for frequent serologic screening (45). Some studies have shown higher seroconversion rates and antibody titers for patients with uremia who were vaccinated before they required dialysis (46). Identification of patients for vaccination early in the course of their renal disease is encouraged.

4. Sexually active homosexual men. Susceptible sexually active homosexual men should be vaccinated regardless of their age or the duration of their homosexual practices. Persons should be vaccinated as soon as possible after their homosexual activity begins. Homosexual and bisexual men known to have HIV infection should be tested for anti-HBs response after completion of the vaccine series and should be counseled accordingly.

5. Users of illicit injectable drugs. All users of illicit injectable drugs who are susceptible to HBV should be vaccinated as early as possible after their drug abuse begins.

6. Recipients of certain blood products. Patients with clotting disorders who receive clotting-factor concentrates have an increased risk of HBV infection. Vaccination is recommended for these persons, and it should be initiated at the time their specific clotting disorder is identified. Prevaccination testing is recommended for patients who have already received multiple infusions of these products.

7. Household and sexual contacts of HBV carriers. Household contacts of HBV carriers are at high risk of HBV infection. Sexual contacts appear to be at greatest risk. When HBV carriers are identified through routine screening of donated blood, diagnostic testing in hospitals, prenatal screening, screening of refugees from certain areas, or other screening programs, they should be notified of their status. All household and sexual contacts should be tested and susceptible contacts vaccinated.

8. Adoptees from countries of high HBV endemicity. Families accepting orphans or unaccompanied minors from countries of high or intermediate HBV endemicity should have the children screened for HBsAg. If the children are HBsAg-positive, family members should be vaccinated (47).

9. Other contacts of HBV carriers. Persons in casual contact with carriers in settings such as schools and offices are at minimal risk of HBV infection, and vaccine is not routinely recommended for them. At child-care centers, HBV transmission between children or between children and staff has rarely been documented. Unless special circumstances exist, such as behavior problems (biting or scratching) or medical conditions (severe skin disease) that might facilitate transmission, vaccination of contacts of carriers in child care is not indicated.

10. Populations with high endemicity of HBV infection. In certain U.S. populations, including Alaskan Natives, Pacific Islanders, and refugees from HBV-endemic areas, HBV infection is highly endemic, and transmission occurs primarily during childhood. In such groups, universal hepatitis B vaccination of infants is recommended to prevent disease transmission during childhood. In addition, more extensive programs of "catch-up" childhood vaccination should be considered if resources are available.

    Immigrants and refugees from areas with highly endemic HBV disease (particularly Africa and eastern Asia) should be screened for HBV markers upon resettlement in the United States. If an HBV carrier is identified, all susceptible household contacts should be vaccinated. Even if no HBV carriers are found within a family, vaccination should be considered for susceptible children less than 7 years of age because of the high rate of interfamilial HBV infection that occurs among these children (48). Vaccination is recommended for all infants of women who were born in areas in which infection is highly endemic.

11. Inmates of long-term correctional facilities. The prison environment may provide a favorable setting for the transmission of HBV because of the use of illicit injectable drugs and because of male homosexual practices. Moreover, it provides an access point for vaccination of percutaneous drug abusers. Prison officials should consider undertaking screening and vaccination programs directed at inmates with histories of high-risk behaviors.

12. Sexually active heterosexual persons. Sexually active heterosexual persons with multiple sexual partners are at increased risk of HBV infection. Risk increases with increasing numbers of sexual partners. Vaccination is recommended for persons who are diagnosed as having recently acquired other sexually transmitted diseases, for prostitutes, and for persons who have a history of sexual activity with multiple partners in the previous 6 months.

13. International travelers. Vaccination should be considered for persons who plan to reside for more than 6 months in areas with high levels of endemic HBV and who will have close contact with the local population. Vaccination should also be considered for short-term travelers who are likely to have contact with blood from or sexual contact with residents of areas with high levels of endemic disease. Ideally, hepatitis B vaccination of travelers should begin at least 6 months before travel to allow for completion of the full vaccine series. Nevertheless, a partial series will offer some protection from HBV infection. The alternative four-dose schedule may provide better protection during travel if the first three doses can be delivered before travel (second and third doses given 1 and 2 months, respectively, after first).

Postexposure Prophylaxis for Hepatitis B

Prophylactic treatment to prevent hepatitis B infection after exposure to HBV should be considered in the following situations: perinatal exposure of an infant born to an HBsAg-positive mother, accidental percutaneous or permucosal exposure to HBsAg-positive blood, sexual exposure to an HBsAg-positive person, and household exposure of an infant less than 12 months of age to a primary care giver who has acute hepatitis B.

Various studies have established the relative efficacies of HBIG and/or hepatitis B vaccine in different exposure situations. For an infant with perinatal exposure to an HBsAg-positive and HBeAg-positive mother, a regimen

combining one dose of HBIG at birth with the hepatitis B vaccine series started soon after birth is 85%-95% effective in preventing development of the HBV carrier state (35, 49-51). Regimens involving either multiple doses of HBIG alone, or the vaccine series alone, have 70%-85% efficacy (52,53).

For accidental percutaneous exposure, only regimens including HBIG and/or IG have been studied. A regimen of two doses of HBIG, one given after exposure and one a month later, is about 75% effective in preventing hepatitis B in this setting (54,55). For sexual exposure, a single dose of HBIG is 75% effective if given within 2 weeks of last sexual exposure (56). The efficacy of IG for postexposure prophylaxis is uncertain. IG no longer has a role in postexposure prophylaxis of hepatitis B because of the availability of HBIG and the wider use of hepatitis B vaccine.

Recommendations on postexposure prophylaxis are based on available efficacy data and on the likelihood of future HBV exposure of the person requiring treatment. In all exposures, a regimen combining HBIG with hepatitis B vaccine will provide both short- and long-term protection, will be less costly than the two-dose HBIG treatment alone, and is the treatment of choice.

Perinatal Exposure and Recommendations

Transmission of HBV from mother to infant during the perinatal period represents one of the most efficient modes of HBV infection and often leads to severe long-term sequelae. Infants born to HBsAg-positive and HBeAg-positive mothers have a 70%-90% chance of acquiring perinatal HBV infection, and 85%-90% of infected infants will become chronic HBV carriers. Estimates are that greater than 25% of these carriers will die from primary hepatocellular carcinoma (PHC) or cirrhosis of the liver (57). Infants born to HBsAg-positive and HBeAg-negative mothers have a lower risk of acquiring perinatal infection; however, such infants have had acute disease, and fatal fulminant hepatitis has been reported (58,59). Based on 1987 data in the United States, an estimated 18,000 births occur to HBsAg-positive women each year, resulting in approximately 4,000 infants who become chronic HBV carriers. Prenatal screening of all pregnant women identifies those who are HBsAg-positive and allows treatment of their newborns with HBIG and hepatitis B vaccine, a regimen that is 85%-95% effective in preventing the development of the HBV chronic carrier state. The following are perinatal recommendations:

1. All pregnant women should be routinely tested for HBsAg during an early prenatal visit in each pregnancy. This testing should be done at the same time that other routine prenatal screening tests are ordered. In special situations (e.g., when acute hepatitis is suspected, when a history of exposure to hepatitis has been reported, or when the mother has a particularly high-risk behavior, such as intravenous drug abuse), an additional HBsAg test can be ordered later in the pregnancy. No other HBV marker tests are necessary for the purpose of maternal screening, although HBsAg-positive mothers identified during screening may have HBV-related acute or chronic liver disease and should be evaluated by their physicians.

2. If a woman has not been screened prenatally or if test results are not available at the time of admission for delivery, HBsAg testing should be done at the time of admission, or as soon as possible thereafter. If the mother is identified as HBsAg-positive greater than 1 month after giving birth, the infant should be tested for HBsAg. If the results are negative, the infant should be given HBIG and hepatitis B vaccine.

3. Following all initial positive tests for HBsAg, a repeat test for HBsAg should be performed on the same specimen, followed by a confirmatory test using a neutralization assay. For women in labor who did not have HBsAg testing during pregnancy and who are found to be HBsAg-positive on first testing, initiation of treatment of their infants should not be delayed by more than 24 hours for repeat or confirmatory testing.

4. Infants born to HBsAg-positive mothers should receive HBIG (0.5 ml) intramuscularly once they are physiologically stable, preferably within 12 hours of birth (Table_4). Hepatitis B vaccine should be administered intramuscularly at the appropriate infant dose. The first dose should be given concurrently with HBIG but at a different site. If vaccine is not immediately available, the first dose should be given as soon as possible. Subsequent doses should be given as recommended for the specific vaccine. Testing

infants for HBsAg and anti-HBs is recommended when they are 12-15 months of age to monitor the success or failure of therapy. If HBsAg is not detectable and anti-HBs is present, children can be considered protected. Testing for anti-HBc is not useful, since maternal anti-HBc can persist for greater than 1 year. HBIG and hepatitis B vaccination do not interfere with routine childhood vaccinations. Breast-feeding poses no risk of HBV infection for infants who have begun prophylaxis.

5. Household members and sexual partners of HBV carriers identified through prenatal screening should be tested to determine susceptibility to HBV infection, and, if susceptible, should receive hepatitis B vaccine.

6. Obstetric and pediatric staff should be notified directly about HBsAg-positive mothers so that neonates can receive therapy without delay after birth and follow-up doses of vaccine can be given. Programs to coordinate the activities of persons providing prenatal care, hospital-based obstetrical services, and pediatric well-baby care must be established to assure proper follow-up and treatment both of infants born to HBsAg-positive mothers and of other susceptible household and sexual contacts.

7. In those populations under U.S. jurisdiction in which hepatitis B infection is highly endemic (including certain Alaskan Natives, Pacific Island groups, and refugees from highly endemic areas accepted for resettlement in the United States), universal vaccination of newborns with hepatitis B vaccine is the recommended strategy for hepatitis B control. HBsAg screening of mothers and use of HBIG for infants born to HBV-carrier mothers may be added to routine hepatitis B vaccination when practical, but screening and HBIG alone will not adequately protect children from HBV infection in endemic areas. In such areas, hepatitis B vaccine doses should be integrated into the childhood vaccination schedule. More extensive programs of childhood hepatitis B vaccination should be considered if resources are available.

Acute Exposure to Blood That Contains (or Might Contain) HbsAg

For accidental percutaneous (needle stick, laceration, or bite) or permucosal (ocular or mucous-membrane) exposure to blood, the decision to provide prophylaxis must include consideration of several factors: a) whether the source of the blood is available, b) the HBsAg status of the source, and c) the hepatitis B vaccination and vaccine-response status of the exposed person. Such exposures usually affect persons for whom hepatitis B vaccine is recommended. For any exposure of a person not previously vaccinated, hepatitis B vaccination is recommended.

Following any such exposure, a blood sample should be obtained from the person who was the source of the exposure and should be tested for HBsAg. The hepatitis B vaccination status and anti-HBs response status (if known) of the exposed person should be reviewed. The outline below and Table_5 summarize prophylaxis for percutaneous or permucosal exposure to blood according to the HBsAg status of the source of exposure and the vaccination status and vaccine response of the exposed person.

For greatest effectiveness, passive prophylaxis with HBIG, when indicated, should be given as soon as possible after exposure (its value beyond 7 days after exposure is unclear).

1. Source of exposure HBsAg-positive

   a. Exposed person has not been vaccinated or has not completed vaccination. Hepatitis B vaccination should be initiated. A single dose of HBIG (0.06 ml/kg) should be given as soon as possible after exposure and within 24 hours, if possible. The first dose of hepatitis B vaccine (Table_3) should be given intramuscularly at a separate site (deltoid for adults) and can be given simultaneously with HBIG or within 7 days of exposure. Subsequent doses should be given as recommended for the specific vaccine. If the exposed person has begun but not completed vaccination, one dose of HBIG should be given immediately, and vaccination should be completed as scheduled.

   b. Exposed person has already been vaccinated against hepatitis B, and anti-HBs response status is known. (1) If the exposed person is known to have had adequate

response in the past, the anti-HBs level should be tested unless an adequate level has been demonstrated within the last 24 months. Although current data show that vaccine-induced protection does not decrease as antibody level wanes, most experts consider the following approach to be prudent.

    a. If anti-HBs level is adequate, no treatment is necessary.

    b. If anti-HBs level is inadequate, ** a booster dose of hepatitis B vaccine should be given.

(2) If the exposed person is known not to have responded to the

primary vaccine series, the exposed person should be given either a single dose of HBIG and a dose of hepatitis B vaccine as soon as possible after exposure, or two doses of HBIG (0.06 ml/kg), one given as soon as possible after exposure and the second 1 month later. The latter treatment is preferred for those who have failed to respond to at least four doses of vaccine.

  c. Exposed person has already been vaccinated against hepatitis B, and the anti-HBs response is unknown. The exposed person should be tested for anti-HBs. (1) If the exposed person has adequate antibody, no additional

treatment is necessary. (2) If the exposed person has inadequate antibody on testing,

one dose of HBIG (0.06 ml/kg) should be given immediately and a standard booster dose of vaccine (Table_3) given at a different site.

2. Source of exposure known and HBsAg-negative

  a. Exposed person has not been vaccinated or has not completed vaccination. If unvaccinated, the exposed person should be given the first dose of hepatitis B vaccine within 7 days of exposure, and vaccination should be completed as recommended. If the exposed person has not completed vaccination, vaccination should be completed as scheduled.

  b. Exposed person has already been vaccinated against hepatitis B. No treatment is necessary.

3. Source of exposure unknown or not available for testing

  a. Exposed person has not been vaccinated or has not completed vaccination. If unvaccinated, the exposed person should be given the first dose of hepatitis B vaccine within 7 days of exposure and vaccination completed as recommended. If the exposed person has not completed vaccination, vaccination should be completed as scheduled.

  b. Exposed person has already been vaccinated against hepatitis B, and anti-HBs response status is known. (1) If the exposed person is known to have had adequate

response in the past, no treatment is necessary. (2) If the exposed person is known not to have responded to the

vaccine, prophylaxis as described earlier in section l.b.(2) under "Source of exposure HBsAg-positive" may be considered if the source of the exposure is known to be at high risk of HBV infection.

  c. Exposed person has already been vaccinated against hepatitis B, and the anti-HBs response is unknown. The exposed person should be tested for anti-HBs. (1) If the exposed person has adequate anti-HBs, no treatment

is necessary. (2) If the exposed person has inadequate anti-HBs, a standard

booster dose of vaccine should be given.

Sexual Partners of Persons with Acute HBV Infection

Sexual partners of HBsAg-positive persons are at increased risk of acquiring HBV infection, and HBIG has been shown to be 75% effective in preventing such infections (56). Because data are limited, the period after sexual exposure during which HBIG is effective is unknown, but extrapolation from other settings makes it unlikely that this period would exceed 14 days. Before treatment, testing of sexual partners for susceptibility is recommended if it does not delay treatment beyond 14 days after last exposure. Testing for anti-HBc is the most efficient prescreening test to use in this population.

All susceptible persons whose sexual partners have acute hepatitis B infection or whose sexual partners are discovered to be hepatitis B carriers should receive a single dose of HBIG (0.06 ml/kg) and should begin the hepatitis B vaccine series if prophylaxis can be started within 14 days of the last sexual contact, or if ongoing sexual contact with the infected person will occur. Giving the vaccine with HBIG may improve the efficacy of postexposure treatment. The vaccine has the added advantage of conferring long-lasting protection.

An alternative treatment for persons who are not from a high-risk group for whom vaccine is routinely recommended and whose regular sexual partners have acute HBV infection is to give one dose of HBIG (without vaccine) and retest the sexual partner for HBsAg 3 months later. No further treatment is necessary if the sexual partner becomes HBsAg-negative. If the sexual partner remains HBsAg-positive, a second dose of HBIG should be given and the hepatitis B vaccine series started.

Household Contacts of Persons with Acute HBV Infection

Since infants have close contact with primary care givers and they have a higher risk of becoming HBV carriers after acute HBV infection, prophylaxis of an infant less than 12 months of age with HBIG (0.5 ml) and hepatitis B vaccine is indicated if the mother or primary care giver has acute HBV infection. Prophylaxis for other household contacts of persons with acute HBV infection is not indicated unless they have had identifiable blood exposure to the index patient, such as by sharing toothbrushes or razors. Such exposures should be treated similarly to sexual exposures. If the index patient becomes an HBV carrier, all household contacts should be given hepatitis B vaccine.

DELTA HEPATITIS

The delta virus (also known as hepatitis D virus (HDV)) is a defective virus that may cause infection only in the presence of active HBV infection. The HDV is a 35- to 37-nm viral particle, consisting of single-stranded RNA (mw 500,000) and an internal protein antigen (delta antigen (HDAg)), coated with HBsAg as the surface protein (5). Infection may occur as either coinfection with HBV or superinfection of an HBV carrier, each of which usually causes an episode of clinical acute hepatitis. Coinfection usually resolves, whereas superinfection frequently causes chronic HDV infection and chronic active hepatitis. Both types of infection may cause fulminant hepatitis.

HDV infection may be diagnosed by detecting HDAg in serum during early infection and by the appearance of total or IgM-specific delta antibody (anti-HDV) during or after infection. A test for detection of total anti-HDV is commercially available. Other tests (HDAg, IgM anti-HDV) are available only in research laboratories.

Routes of transmission of HDV are similar to those of HBV. In the United States, HDV infection most commonly affects persons at high risk of HBV infection, particularly parenteral drug abusers and persons with hemophilia.

Since HDV is dependent on HBV for replication, prevention of hepatitis B infection, either preexposure or postexposure, will suffice to prevent HDV infection for a person susceptible to hepatitis B. Known episodes of perinatal, sexual, or percutaneous exposure to serum or exposure to persons known to be positive for both HBV

and HDV should be treated exactly as such exposures to HBV alone.

Persons who are HBsAg carriers are at risk of HDV infection, especially if they participate in activities that put them at high risk of repeated exposure to HBV (parenteral drug abuse, male homosexual activity). However, at present no products are available that might prevent HDV infection in HBsAg carriers either before or after exposure.

NON-A, NON-B HEPATITIS

Parenterally Transmitted (PT) Non-A, Non-B Hepatitis

Parenterally transmitted non-A, non-B hepatitis accounts for 20%-40% of acute viral hepatitis in the United States and has epidemiologic characteristics similar to those of hepatitis B (60). Recently, a portion of the genome of a virus thought to be responsible for PT non-A, non-B hepatitis was cloned (2). A candidate serologic assay for antibody to this virus (proposed as hepatitis C virus) has been developed. This assay appears to detect a substantial number of persons with chronic infection and is being evaluated for screening potential blood donors (3). Although PT non-A, non-B hepatitis has traditionally been considered a transfusion-associated disease, most reported cases have not been associated with blood transfusion (61-64). Groups at high risk of acquiring this disease include transfusion recipients, parenteral drug users, and dialysis patients (62,63). Health-care work that entails frequent contact with blood, personal contact with others who have had hepatitis in the past, and contact with infected persons within households have also been documented in some studies as risk factors for acquiring PT non-A, non-B hepatitis (63-65). However, the role of person-to-person contact in disease transmission has not been well defined, and the importance of sexual activity in the transmission of this type of hepatitis is unclear.

Multiple episodes of non-A, non-B hepatitis have been observed among the same individuals and may be due to different bloodborne agents. An average of 50% of patients who have acute PT non-A, non-B hepatitis infection later develop chronic hepatitis (66). Experimental studies of chimpanzees have confirmed the existence of a carrier state, which may be present in 1%-3% of the population (67,68).

The risk and consequences of perinatal transmission of PT non-A, non-B hepatitis are not well defined. Only one small study has been published in which infants born of 12 women who had acute PT non-A, non-B hepatitis during pregnancy were followed. Six infants developed transient alanine aminotransferase (ALT) elevations at 4-8 weeks of age (69).

The results have been equivocal in several studies attempting to assess the value of prophylaxis with IGs against PT non-A, non-B hepatitis (70-72). For persons with percutaneous exposure to blood from a patient with PT non-A, non-B hepatitis, it may be reasonable to administer IG (0.06 ml/kg) as soon as possible after exposure. In other circumstances, no specific recommendations can be made.

Enterically Transmitted (ET) Non-A, Non-B Hepatitis

A distinct type of non-A, non-B hepatitis acquired by the fecal-oral route was first identified through investigations of large waterborne epidemics in developing countries. This ET non-A, non-B hepatitis, which has occurred in epidemics or sporadically in parts of Asia, North and West Africa, and Mexico, is serologically distinct from other known hepatitis viruses (4,73). Young to middle-aged adults are most often affected, with an unusually high mortality among pregnant women. The disease has been transmitted to experimental animals, and candidate viruses have been identified; however, no serologic tests have yet been developed (74).

ET non-A, non-B hepatitis has not been recognized as an endemic disease in the United States or Western Europe, and it is unknown whether the causative agent is present in these areas. Cases have been documented, however, among persons returning from travel to countries in which this disease occurs (75).

Travelers to areas having ET non-A, non-B hepatitis may be at some risk of acquiring this disease by close contact with infected persons or by consuming contaminated food or water. There is no evidence that U.S.-manufactured IG will prevent this infection. As with hepatitis A and other enteric infections, the best means of

preventing ET non-A, non-B hepatitis is avoiding potentially contaminated food or water.

- An adequate antibody response is greater than or equal to 10 milliInternational Units (mIU)/ml, approximately equivalent to 10 sample ratio units (SRU) by RIA or positive by enzyme immunoassay (EIA), measured 1-6 months after completion of the vaccine series. ** An adequate antibody level is greater than or equal to 10 milliInternational Units (mIU)/ml, approximately equivalent to 10 sample ratio units (SRU) by RIA or positive by EIA.

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Protection Against Viral Hepatitis Recommendations of the Immunization Practices Advisory Committee (ACIP)

Table_1

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

```
Table 1. Hepatitis nomenclature
================================================================================
              Abbreviation   Term                 Definition/Comments
--------------------------------------------------------------------------------
A. Hepatitis A  HAV          Hepatitis A virus    Etiologic agent of "infectious" hepatitis; a
                                                  picornavirus; single serotype.

                Anti-HAV     Antibody to HAV      Detectable at onset of symptoms; lifetime
                                                  persistence.

                IgM          IgM class antibody   Indicates recent infection with hepatitis A;
                anti-HAV     to HAV               detectable for 4-6 months after infection.

B. Hepatitis B  HBV          Hepatitis B virus    Etiologic agent of "serum" hepatitis; also known
                                                  as Dane particle.

                HBsAg        Hepatitis B surface  Surface antigen(s) of HBV detectable in large
                             antigen              quantity in serum; several subtypes identified.

                HBeAg        Hepatitis B e antigen Soluble antigen; correlates with HBV replication,
                                                  high titer HBV in serum, and infectivity of serum.

                HBcAG        Hepatitis B core antigen No commercial test available.

                Anti-HBs     Antibody to HBsAg    Indicates past infection with and immunity to
                                                  HBV, passive antibody from HBIG, or immune
                                                  response from HB vaccine.

                Anti-HBe     Antibody to HBeAg    Presence in serum of HBsAg carrier indicates
                                                  lower titer of HBV.

                Anti-HBc     Antibody to HBcAg    Indicates prior infection with HBV at some
                                                  undefined time.

                IgM          IgM class antibody   Indicates recent infection with HBV; detectable for
                anti-HBc     to HBcAg             4-6 mos. after infection.

C. Delta        HDV          Hepatitis D virus    Etiologic agent of delta hepatitis; can cause
hepatitis                                         infection only in presence of HBV.

                HDAg         Delta antigen        Detectable in early acute delta infection.

                Anti-HDV     Antibody to delta antigen Indicates present or past infection with delta
                                                  virus.

D. Non-A,       PT-NANB      Parenterally transmitted Diagnosis by exclusion. At least two candidate
non-B                                             viruses, one of which has been proposed as
hepatitis                                         hepatitis C virus; shares epidemiologic features
                                                  with hepatitis B.

                ET-NANB      Enterically transmitted Diagnosis by exclusion. Causes large epidemics
                                                  in Asia, Africa, and Mexico; fecal-oral or
                                                  waterborne.

E. Immune       IG           Immune globulin (previously Contains antibodies to HAV, low-titer antibodies
globulins                    ISG, immune serum globulin, to HBV.
                             or gamma globulin)

                HBIG         Hepatitis B immune globulin Contains high-titer antibodies to HBV.
--------------------------------------------------------------------------------
================================================================================
```

Table_2

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

```
Table 2. Prevalence of hepatitis B serologic markers in various population groups
================================================================================
                                          Prevalence of serologic markers
                                                 of HBV infection
                                          -------------------------------
Population group                          HBsAg (%)    Any marker (%)
--------------------------------------------------------------------------------
Immigrants/refugees from areas of
  high HBV endemicity                        13            70-85

Alaskan Natives/Pacific Islanders           5-15           40-70

Clients in institutions for the developmentally
  disabled                                  10-20          35-80

Users of illicit parenteral drugs            7             60-80

Sexually active homosexual men               6             35-80

Household contacts of HBV carriers          3-6            30-60

Patients of hemodialysis units              3-10           20-80

Health-care workers --
```

```
  frequent blood contact                      1-2        15-30

Prisoners (male)                              1-8        10-80

Staff of institutions for the developmentally
  disabled                                    1          10-25

Heterosexuals with multiple partners          0.5        5-20

Health-care workers --
  no or infrequent blood contact              0.3        3-10

General population (NHANES II) *
  Blacks                                      0.9        14
  Whites                                      0.2         3
--------------------------------------------------------------------------
* Second National Health and Nutrition Examination Survey (26).
==========================================================================
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Table_3
Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

```
Table 3. Recommended doses and schedules of currently licensed HB vaccines
=============================================================================================================
                                         Vaccine
                    ---------------------------------------------------------------------------
                     Heptavax-B *,+        Recombivax HB *         Engerix-B *,&
Group               Dose (ug)  (ml)      Dose (ug)  (ml)        Dose (ug)  (ml)
                    ---------------------------------------------------------------------------
Infants of HBV-carrier mothers    10    (0.5)        5     (0.5)         10      (0.5)

Other infants and children <11 years   10  (0.5)     2.5   (0.25)        10      (0.5)

Children and adolescents 11-19 years    20  (1.0)     5     (0.5)         20      (1.0)

Adults > 19 years                 20    (1.0)        10    (1.0)         20      (1.0)

Dialysis patients and other       40    (2.0) @      40    (1.0) **      40      (2.0) @,++
  immunocompromised persons
                    ---------------------------------------------------------------------------
 * Usual schedule: three doses at 0, 1, 6 months.
 + Available only for hemodialysis and other immunocompromised patients and for persons with known allergy to
   yeast.
 & Alternative schedule: four doses at 0, 1, 2, 12 months.
 @ Two 1.0-ml doses given at different sites.
** Special formulation for dialysis patients.
++ Four-dose schedule recommended at 0, 1, 2, 6 months.
=============================================================================================================
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Table_4
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```
Table 4. Hepatitis B virus postexposure recommendations
=============================================================================================================
                         HBIG                                    Vaccine
           -----------------------------------------    -----------------------------------------
Exposure   Dose          Recommended timing             Dose         Recommended timing
           -----------------------------------------    -----------------------------------------
Perinatal  0.5 ml IM     Within 12 hours of birth       0.5 ml IM *  Within 12 hours of birth +

Sexual     0.06 ml/kg IM Single dose within 14 days     1.0 ml IM *  First dose at time of
                         of last sexual contact                      HBIG treatment +
           -----------------------------------------    -----------------------------------------
* For appropriate age-specific doses of each vaccine, see Table 3.
+ The first dose can be given the same time as the HBIG dose but in a different site; subsequent doses should be
  given as recommended for specific vaccine.
=============================================================================================================
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Table_5
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```
Table 5. Recommendations for hepatitis B prophylaxis following percutaneous or permucosal
exposure
=============================================================================================================
                                       Treatment when source is found to be:
           -----------------------------------------------------------------------------------
```

Protection Against Viral Hepatitis Recommendations of the Immunization Practices Advisory Committee (ACIP)

```
                                                           Source not tested
Exposed person        HBsAg-positive        HBsAg-negative    or unknown
------------------------------------------------------------------------------------
Unvaccinated          HBIG x 1 * and        Initiate HB vaccine +  Initiate HB vaccine +
                      initiate HB vaccine +

Previously vaccinated Test exposed for anti-Hbs  No treatment      No treatment

  Known responder     1. If adequate, & no treatment
                      2. If inadequate, HB vaccine
                         booster dose

  Known nonresponder  HBIG x 2 or           No treatment      If known high-risk source,
                      HBIG x 1 plus 1 dose                    may treat as if source
                      HB vaccine                              were HBsAg-positive

  Response unknown    Test exposed for anti-Hbs  No treatment  Test exposed for anti-HBs

                      1. If inadequate, &                      1. If inadequate &, HB
                         HBIG x 1 plus HB vaccine                 vaccine booster dose
                         booster dose                         2. If adequate, no treatment
                      2. If adequate, no treatment
------------------------------------------------------------------------------------
* HBIG dose 0.06 ml/kg IM.
+ HB vaccine dose -- see Table 3.
& Adequate anti-HBs is >= 10 SRU by RIA or positive by EIA.
====================================================================================
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Page converted: 08/05/98

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This page last reviewed 5/2/01