APPENDIX 6

MORBIDITY AND MORTALITY WEEKLY REPORTS

CONTENTS

CENTERS FOR DISEASE CONTROL

December 16, 1983/Vol. 32/No. 2S

MMWR Supplement

MORBIDITY AND MORTALITY WEEKLY REPORT

VIRAL HEMORRHAGIC FEVER:

INITIAL MANAGEMENT OF SUSPECTED AND CONFIRMED CASES

U.S. Department of Health and Human Services
Public Health Service
Centers for Disease Control
Center for Infectious Diseases
Division of Viral Diseases
Atlanta, Georgia 30333

Viral Hemorrhagic Fever: Initial Management of Suspected and Confirmed Cases

INTRODUCTION

Every year the possibility exists that travelers with viral hemorrhagic fever (VHF) transmissible from person to person—Lassa, Ebola, Marburg, or Crimean-Congo hemorrhagic fever (CCHF)—may enter the United States. Among U.S. citizens, health professionals involved in the care of patients in Africa might be most likely to be exposed to agents of these diseases. Serologic studies have indicated, however, that missionaries and Peace Corps volunteers serving in Africa without obvious or frequent exposure to ill persons may also be exposed. Additionally, travelers may enter the United States asymptomatically infected with one of these viruses. Laboratory-acquired infection also remains a possibility in research or diagnostic facilities. Since guidelines concerning the approach to suspected cases of VHF were last published, in 1980 (*1*), approximately four cases of illness suspected of being VHF have occurred in the United States each year. None have been confirmed as VHF.

Although the source in nature of two (Ebola and Marburg) of the four viruses discussed in this document remains unknown, all four are capable of being transmitted from person to person, especially in the hospital setting. The communicability of these viruses in hospitals may vary considerably; however, the consequences of such transmission may be severe since case-fatality rates in hospital outbreaks have been high. The potential danger is increased by the fact that these illnesses begin with nonspecific symptoms that may be confused with other diseases. Therefore, appropriate barrier techniques designed to prevent transmission may not be instituted until late in the course of these illnesses, if at all. Finally, the lack of experience with these agents in the United States understandably results in confusion and anxiety on the part of physicians and other hospital personnel when a suspected importation occurs.

Since the earlier guidelines were published, additional clinical and laboratory observations have produced new information on the agents causing VHF and the illnesses they produce. Also, new information is available on treating patients with VHF. These guidelines are therefore offered to provide up-to-date information on these diseases, an organized approach to the suspected case of VHF, and guidelines concerning the handling of specimens and the care of patients. Also, a current list of persons available for consultation at CDC is included below. Because Lassa, Ebola, Marburg, and CCHF are the only hemorrhagic fevers for which person-to-person transmission has been documented, these guidelines will be limited to these four diseases. The reader is referred elsewhere for discussion of other agents that cause VHF in humans (*2*).

Further information and advice about the management of the patient with suspected VHF, control measures, and collection and shipment of diagnostic specimens are available on request from the following persons at CDC, Atlanta, Georgia. For all telephone numbers, dial 404-329 + extension:

1. Chief, Special Pathogens Branch, Division of Viral Diseases, Center for Infectious Diseases: Joseph B. McCormick, M.D. (ext. 3308).
2. Medical Epidemiologist, Office of the Director, Division of Viral Diseases, Center for Infectious Diseases: Jonathan E. Kaplan, M.D. (ext. 3095).
3. Director, Division of Viral Diseases, Center for Infectious Diseases: Frederick A. Murphy, D.V.M.(ext. 3574).
4. Acting Director, Office of Biosafety: John E. Forney, Ph.D. (ext. 3885).
5. After regular office hours and on weekends, the above-mentioned staff members may be contacted through the CDC duty officer (ext. 2888).

LASSA FEVER

Lassa fever first came to medical attention in 1969 when three nurses working in missionary hospitals in Nigeria became ill. Two died in Nigeria, and the third patient, who was transported to the United States while still ill, survived (*3*). Two persons who worked in the laboratory in the United States where virologic studies were being done also became ill; one had worked with tissue cultures and infected mice, while the other had no known contact with the virus (*4,5*). Since that time Lassa fever has been shown to be endemic in many areas of West and Central Africa (*6*). The reservoir of infection, which is caused by an arenavirus, is the multimammate rat *Mastomys natalensis*. This rodent inhabits rural areas in sub-Saharan Africa and lives in and around human dwellings (*6, 7*).

Persons presumably acquire naturally occurring infections by contact with *M. natalensis*, either through handling the animal directly or by inhaling aerosolized excretions, such as urine. Subsequently, person-to-person transmission may occur within households and hospitals. Although one experience in Jos, Nigeria, has suggested that airborne transmission may occur (*8*), it is generally believed that direct contact with a patient or overt exposure to infective tissues, secretions, or excretions is necessary to transmit the infection from person to person.

The severity of illness appears to depend on the mode of transmission of the virus. Thus, in the community, where rodent-to-human transmission accounts for a substantial proportion of cases, the case-to-infection ratio may be as low as 1:30 (*9*). In the hospital, however, where transmission may occur by direct contact with infected secretions, excretions, or tissues, including inoculation with contaminated needles, this ratio is undoubtedly much higher. Case-fatality rates have ranged from 14% for sporadic cases in areas with endemic disease (*10*) to 52% for nosocomial outbreaks (*8*).

The incubation period of Lassa fever ranges from 6 to 21 days. Illness is usually heralded by fever, headache, myalgia, sore throat, and cough; chest and abdominal pain are also frequent complaints. In severe cases encephalopathy, hemorrhage, and shock may occur. Diagnosis can be made in three ways: by demonstrating a fourfold rise in titer of antibody to Lassa virus between acute-phase and convalescent-phase serum specimens with the indirect fluorescent antibody (IFA) technique, by detecting Lassa immunoglobulin M (IgM) antibodies, or by isolating Lassa virus from blood, urine, or throat (see HANDLING AND TRANSPORTING OF LABORATORY SPECIMENS). The diagnosis of Lassa is unlikely if no IgM or immunoglobulin G (IgG) antibody is detectable by the 14th day of illness, or if no virus is isolated from blood obtained during the first 7 days of illness. Virus isolation should be attempted only at laboratories equipped to handle viruses assigned to Biosafety Level 4 (*11*).

Treatment of Lassa fever is supportive and includes restoration of blood losses and maintenance of plasma volume, blood pressure, and electrolyte balance. Although immune plasma obtained from survivors of the disease has been used in severe cases, there are no data to confirm its efficacy. Preliminary data suggest that ribavirin, an antiviral compound, may be useful in the early stage of the illness (*12*). No Lassa fever vaccine is available.

Since the first recognized cases of Lassa fever in the United States in 1969, there has been one additional imported case of Lassa in this country, in 1976 (*13*). No secondary transmission following this case was noted despite intensive surveillance of close contacts. At least eight additional importations of Lassa fever have occurred in countries without endemic disease since recognition of the disease; however, no secondary transmission was identified after any of these importations (*14-20*). In four of these instances (*15, 18-20*), the possibility of Lassa fever was not entertained until late in the course of illness or until after the patient had recovered, and barrier nursing techniques were not used during the acute stage of illness.

EBOLA HEMORRHAGIC FEVER

Ebola hemorrhagic fever came to medical attention in 1976 when successive outbreaks occurred in Sudan and Zaire, comprising over 500 cases (*21,22*). The Sudan outbreak involved workers at a cotton factory, with subsequent spread in a hospital. Nosocomial transmission was associated with direct patient contact, and particularly with nursing a patient (*21*). The Zaire outbreak centered around an outpatient facility; contaminated needles were involved in disseminating infection in nearly half the cases (*22*). The case-fatality rates in these two outbreaks were 53% and 88%, respectively. A smaller outbreak (34 cases) was investigated in Sudan in 1979 (*23*). Serologic studies suggest that Ebola fever is endemic in limited areas of Sudan and Zaire, as well as the Central African Republic and Kenya (*24,25*). Both the reservoir of the virus in nature and the source of human infection remain unknown. Classification of Ebola virus in the family Filoviridae has been proposed (*26*).

Once Ebola infection develops in humans, person-to-person transmission may occur, both in the community and in the hospital. Intrafamilial spread outside the hospital appears to be related to close personal contact with a case (*22,23*); within the hospital, injections with contaminated needles have been implicated as well (*22*). Evidence suggests that airborne transmission is not important in the spread of Ebola infection (*21-23*).

The case-to-infection ratio of Ebola fever is unknown, but serologic studies suggest that mild or inapparent infection may be common in areas with endemic disease (*21,22*). Person-to-person transmission in medical facilities may result in a higher case-to-infection ratio (*22*). Case-fatality rates may be extremely high, as illustrated by the experiences in Zaire and Sudan (*21,22*).

The average incubation period of Ebola fever is estimated to be 6-9 days, with a range of 2-21 days. Ebola illness begins with sudden onset of fever, accompanied by headache, myalgia, sore throat, abdominal pain, and diarrhea. A maculopapular skin rash is commonly seen in fair-skinned patients. Hemorrhage, usually from the gastrointestinal (GI) tract, is very common. The diagnosis can be made serologically by the IFA test or, preferably, by isolation of Ebola virus from the blood in the acute phase of illness. As with Lassa fever, the diagnosis of Ebola fever is unlikely if virus is not isolated from blood obtained during the first 7 days of illness, or if antibody is not present by the 14th day of illness.

Treatment of Ebola illness is supportive. Immune plasma may be effective in reducing the level of viremia (*27*), but controlled studies to evaluate its effect on the outcome of illness have not been done. Evidence suggests that there is no cross-protection between the Zaire and Sudan strains of the virus (*28*), so immune plasma may have to be specific to be effective. No studies with ribavirin or other antiviral compounds have been undertaken.

There have been no documented imported cases of Ebola fever in the United States or Europe. However, one laboratory-acquired infection occurred in Great Britain in 1976 following accidental inoculation with infected guinea pig tissue (*29*); the patient survived, and no secondary transmission was detected (*30*).

MARBURG VIRUS DISEASE

Marburg virus disease first came to medical attention in 1967 when 31 persons became ill in Europe following the importation of a group of African green monkeys from Uganda (*31-33*). Twenty-five of these patients were exposed directly to tissues from the monkeys. Six secondary cases occurred, all in persons who had direct contact with patients or their tissues. In 1975, a hitchhiker acquired Marburg infection in Rhodesia and then transmitted it to his girlfriend. She, in turn, transmitted it to a nurse in South Africa with whom she shared cigarettes, coffee cups, and handkerchiefs (*34,35*). A third outbreak of Marburg disease involved one primary and one secondary case (in the attending physician) in Kenya in 1980 (*36*), and a fourth involved a single case in South Africa in 1982 (*37*). Despite intensive investigation of these outbreaks, no natural reservoir of the Marburg virus has been identified, and the

area of endemicity has not been well defined. Morphologically, Marburg virus resembles the Ebola agent, but it is antigenically distinct. Classification in the family Filoviridae has been proposed (*26*).

Person-to-person transmission of Marburg disease has occurred in three of the four outbreaks that have been investigated. In each of these situations, transmission resulted from direct contact with an infected animal, an infected human, or infected tissues; there has been no evidence of airborne person-to-person transmission. The case-to-infection ratio of Marburg disease is unknown, but the case-fatality rate in the reported outbreaks has been 26%.

After an incubation period of 3-9 days, Marburg disease is heralded by fever, headache, myalgia, sore throat, dysphagia, vomiting, and diarrhea. A maculopapular skin rash is extremely common. Hemorrhage, usually from the GI tract, is a frequent finding, and disseminated intravascular coagulation (DIC) has been implicated in its pathogenesis. Diagnosis is made by IFA testing of serum specimens or by isolation of the virus from blood. As with Lassa and Ebola viruses, the diagnosis of Marburg virus disease is unlikely if virus is not isolated from blood obtained during the first 7 days of illness, or if antibody is not present by the 14th day of illness.

Treatment of Marburg virus disease is supportive. Immune plasma has been used, but its efficacy is unknown. Heparin may be useful in preventing DIC (*35*). No studies have evaluated the use of antiviral compounds in this disease.

Since the original Marburg disease outbreak, there have been no known cases of Marburg disease, either imported or laboratory acquired, in Europe or the United States.

CRIMEAN-CONGO HEMORRHAGIC FEVER

Crimean hemorrhagic fever was first described in 1945, following an epidemic among field workers in the Crimea in the Soviet Union. The agent was isolated in 1945 (*38*), and subsequent studies showed that it was identical to a virus isolated in the Congo in 1956 (*39*); hence, the name Crimean-Congo hemorrhagic fever (CCHF). The disease is now known to be endemic throughout Eastern Europe, Africa, and Asia (*38*). Its natural reservoir is wild and domesticated mammals such as sheep, cattle, goats, and hares. Over 20 species of ticks have been found to be infected; however, illness is usually transmitted to humans by the bite of an ixodid (hard) tick of the genus *Hyalomma* (*38*). The CCHF agent has been classified as a bunyavirus.

Once a case of human CCHF occurs, person-to-person transmission is possible, particularly in the hospital setting; nosocomial outbreaks have occurred in several countries in which the disease is endemic, including the Soviet Union, Pakistan, India, and Iraq (*38,40-42*). Transmission is presumed to occur by direct contact with infective blood (*38,40,41*). There are no data to suggest that airborne transmission is an important mode of spread. The case-to-infection ratio in CCHF is unknown, but mild and inapparent infections do occur (*43*). The case-fatality rate ranges from 15% among sporadic cases (*43*) to 70% in nosocomial outbreaks (*42*).

After an incubation period of 3-6 days, illness is heralded by fever, chills, headache, myalgia, abdominal pain, and vomiting. Hemorrhage is a hallmark of the disease, and vascular collapse is common. Diagnosis is made serologically by the complement-fixation, indirect-hemagglutination, or IFA tests, or by isolation of the virus from blood. Failure to detect antibody by the 20th day of illness (the antibody response in CCHF may be delayed compared with that in other VHFs) or failure to isolate virus from blood obtained during the first 7 days of illness render the diagnosis unlikely.

Treatment is supportive. Although Suleiman (*41*) gained the impression that immune plasma may be effective, studies testing the efficacy of immune plasma have been inconclusive (*38*). The use of antiviral agents in CCHF has not been investigated.

No imported or laboratory-acquired cases of CCHF have been documented in countries without endemic disease.

APPROACH TO A SUSPECTED CASE OF VHF

When confronted with a possible case of VHF, a physician should ask three questions: 1) Where has the patient been? 2) What time has elapsed between the patient's presence in the area with endemic VHF, or exposure to a person with VHF, and onset of illness? 3) What are the patient's symptoms? Careful history of the exact location of travel should be obtained. It is important to note that within the areas endemic for the various VHFs (Table 1), only specific types of exposure—direct or indirect contact with local animals or direct contact with ill persons or their tissues, secretions, or excretions—indicate the possibility of VHF. The vast majority of Americans visiting Africa and other areas with endemic VHFs will offer no history compatible with exposure to the organisms that cause VHF. Also, most travelers to urban areas, even though they may occasionally visit a rural area, will not come into contact with the virus reservoirs. An interval in excess of 3 weeks between possible exposure to VHF and onset of illness makes the diagnosis of VHF unlikely (Table 1). Since patients with VHF may present with nonspecific symptoms (fever, headache, myalgia), clinical diagnosis is very difficult, if not impossible. However, certain symptoms and signs in addition to these three (pharyngitis, conjunctivitis, vomiting, diarrhea, abdominal pain, and, most important, hemorrhagic manifestations and/or shock) should suggest the possibility of VHF (Table 1). Other febrile illnesses—malaria, typhoid fever, meningococcemia, arboviral and enteroviral infections, and leptospirosis—must be considered in the differential diagnosis.

If, having taken into account the above considerations, the physician feels the patient may have VHF, he/she should take the following actions immediately: 1) Place the patient in strict isolation, and 2) contact the local and state health departments and CDC.

ISOLATION OF PATIENTS WITH SUSPECTED AND CONFIRMED VHF

Ideally, patients with suspected or confirmed VHF should be immediately placed in a special isolation unit (such as a Vickers Bed Isolator*) designed to prevent contamination of the area outside of the patient's immediate environment. Realistically, VHF will probably be suspected or diagnosed most frequently in medical facilities that have no specialized containment rooms or Vickers Isolators available. Most hospitals in the United States, however, have rooms in which it is possible to create negative pressure compared with the outside hall and in which air can be exhausted without recirculation to other rooms. Under these circumstances, strict isolation (*44*) should prevent transmission to others. If possible, the patient should remain in the hospital in which he/she is initially seen. If appropriate isolation cannot be arranged in this hospital, or if the hospital staff is logistically unprepared to care for a patient with VHF, transporting the patient to another institution, preferably a local one, must be considered. However, the risk to paramedical personnel and, more important, to the patient whose medical care will be delayed must be weighed carefully in making such a decision. It is recommended that the local and state health departments or CDC be consulted about the decision to move the patient to another institution and the means by which this may be accomplished.

To minimize the risk of transmitting VHF to health personnel caring for the patient, a number of precautions should be instituted:

1. The patient should be placed in a private room that is suitable for strict isolation and that can only be entered through an anteroom. Air from the patient's room should be at negative pressure compared with that of the outside hall, and it should be discharged without recirculation (the hospital engineer should confirm this before the room is used).

2. The anteroom, which should have hand-washing facilities, should be allocated for use by persons entering and leaving the patient's room. Air from this anteroom also should not recirculate to other parts of the hospital. The anteroom should contain supplies required for day-to-day care of the patient and supplies required for decontamination of materials taken from the patient's room (see Appendix).

*Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

Table 1. Clinical and epidemiologic characteristics of viral hemorrhagic fever

Characteristic	Lassa fever	Ebola hemorrhagic fever	Marburg virus disease	Crimean-Congo hemorrhagic fever
Endemic areas	West Africa (Guinea to Central Africa)	East Africa (Zaire, Sudan, Central African Republic, Kenya)	East Africa, South Africa	Eastern Europe, Asia, Africa
Etiologic-agent classification	Arenaviridae	Filoviridae (proposed)	Filoviridae (proposed)	Bunyaviridae
Reservoir in nature	Rodents (*Mastomys natalensis*)	?	?	Ticks (*Hyalomma* genus and others), wild and domesticated mammals
Modes of transmission	Rodent-to-human (virus excreted in urine); person-to-person	? Person-to-person	? Person-to-person	Tick bite; Person-to-person
Incubation period	6-21 days	2-21 days	3-9 days	3-6 days
Symptoms	**% of cases**	**% of cases**	**% of cases**	**% of cases**
Headache	50-75	75-100	75-100	75-100
Myalgia	25-50	75-100	50-75	50-75
Sore throat	75-100	75-100	50-75	25-50
Cough	50-75	25-50	5-25	25-50
Dysphagia	5-25	5-25	25-50	
Vomiting	75-100	50-75	75-100	75-100
Diarrhea	25-50	75-100	75-100	25-50
Chest pain	25-50	50-75	5-25	5-25
Abdominal pain	50-75	75-100	5-25	75-100
Signs				
Fever	75-100	75-100	75-100	75-100
Conjunctivitis	25-50	50-75	25-50	5-25
Pharyngitis	75-100	25-50	5-25	25-50
Cervical lymphadenopathy	25-50		25-50	
Abdominal tenderness	50-75	25-50		25-50
Skin rash (macular)	5-25	50-75	75-100	
Hemorrhage (skin or gastrointestinal)	25-50	75-100	25-50	75-100
Shock	25-50	25-50	25-50	50-75
Laboratory				
Leukopenia	25-50	5-25	75-100	50-75
Thrombocytopenia			75-100	75-100
Proteinuria	50-75	50-75		50-75
Disseminated intravascular coagulation			5-25	5-25

3. The external surfaces of all containers should be decontaminated before they are removed from the anteroom. Disposable linen, pajamas, and protective clothing worn by persons entering the patient's room (see below) should be double bagged in airtight bags, and the outside bag should be sponged with 0.5% sodium hypochorite solution (10% aqueous solution of household bleach) or a suitable phenolic disinfectant (such as Lysol®) before being removed from the anteroom. The bag and its contents should then be incinerated. Disposable items used in patient care/management, especially those involved in obtaining laboratory specimens (see HANDLING AND TRANSPORTING OF LABORATORY SPECIMENS) should be placed in a rigid plastic container containing 0.5% sodium hypochlorite. The outside of this container should be sponged with 0.5% sodium hypochlorite or a phenolic disinfectant before being removed from the patient's room. The container should then be autoclaved and discarded or incinerated.

4. Hospital traffic past the anteroom should be minimized, preferably by locating the room at the end of a corridor, and the door of the anteroom should be kept closed. A daily log should be kept of all persons entering the patient's room (the log should include adequate information for contacting these persons).

5. All persons entering the patient's room should wear the following disposable items: gowns, face masks, goggles, gloves, and head and shoe covers. Some persons may prefer to use full-face respirators equipped with high-efficiency particulate air (HEPA) filters, or nose and mouth respirators with HEPA filters plus goggles or face shield. These items may be stored either in the anteroom or immediately outside the door to the anteroom in the hallway. Protective clothing should be removed by the individual before he/she emerges from the anteroom into the outside hallway.

6. Routine management of the patient should be organized to limit traffic, including that of medical and nursing staff, into and out of the room. Patients who are ambulatory and have few symptoms should be encouraged to take care of themselves as much as possible (for example, noting their routine vital signs and making their beds).

7. The patient should use a chemical toilet, and all bodily secretions and excretions should be treated with 0.5% sodium hypochlorite before being removed from the room.

VERIFICATION OF THE DIAGNOSIS OF VHF

Diagnosis of VHF can be confirmed by isolation of the causative virus from the blood of the patient or, in the case of Lassa fever, from the throat or urine. Diagnosis may also be made serologically, although antibodies are not usually present until the second week of illness. The Mobile Laboratory (see below) is equipped to perform serologic testing for the agents under discussion, but virus isolation must be done at a laboratory with appropriate containment facilities. The following guidelines pertain to obtaining the appropriate specimens for virus isolation.

HANDLING AND TRANSPORTING OF LABORATORY SPECIMENS

Collecting Specimens

The following initial specimens should be taken to confirm or rule out a diagnosis of VHF:

1. A throat swab placed in a plastic, screw-cap container in 1 ml of sterile, phosphate-buffered neutral saline, containing 1% human serum albumin or 25% rabbit serum albumin.

2. A clean-catch, midstream urine specimen obtained in a sterile container. Five milliliters of urine should be stabilized by the addition of either human serum albumin to a final concentration of 1% or rabbit serum albumin to a final concentration of 25% and placed in a plastic, screw-cap container.

3. Venous blood for antibody studies and virus isolation. Ten milliliters of clotted blood should be obtained in a sealed, plastic tube, if available (using vacutainers simplifies collection of multiple samples but may require using glass collection tubes). When obtaining the blood specimen, personnel should be acutely aware of the danger of accidental inoculation and of

sprays, spills, or aerosols (this obviously pertains to all specimens obtained from the patient for diagnostic purposes). Personnel should not attempt to replace the plastic needle guard on a used needle, but should discard the needle and syringe (or needle and vacutainer sleeve) into a rigid plastic container containing 0.5% sodium hypochlorite. The container should then be autoclaved and discarded or incinerated. To avoid unnecessary exposure of laboratory personnel, the blood specimen should not be centrifuged or separated.

The outside of each specimen container should be swabbed with 0.5% sodium hypochlorite or a phenolic disinfectant, and a label should be affixed with the patient's name, the date of the specimen, and the nature of the suspected infection. Specimens should then be double bagged in airtight bags and labeled similarly. Bags containing specimens should be sponged with a solution of 0.5% sodium hypochlorite or a phenolic disinfectant before being taken from the room.

Packaging and Transporting Specimens

CDC (Office of Biosafety or contacts listed in the Introduction) or the state health department should be contacted for instructions on packaging, labeling, and shipping diagnostic laboratory specimens since shipment is subject to the applicable provisions of the Public Health Service interstate quarantine regulations (*45*). In general, specimens should be packaged as follows:

1. Place the specimen in a securely closed, watertight, primary container (screw-cap plastic test tube or vial), and seal the cap with tape. Heat-sealed plastic vials are also ideal primary containers for etiologic agents, provided they are formulated from a plastic that is not prone to shatter at temperatures of -20 C or lower.
2. Wrap the primary container with sufficient absorbent material (for example, paper towels or tissue) to absorb the entire contents in case the container breaks or leaks.
3. Place the wrapped, sealed primary container in a durable, watertight secondary container (screw-cap metal mailing tube or sealed metal can). Screw-cap metal mailing tubes should be sealed with tape. Several primary containers of specimens, each individually wrapped in absorbent material, may be placed in the secondary container, provided that the secondary container does not contain more than 50 ml of specimen material.
4. On the outside of the secondary container, place the specimen data forms, letters, and other information identifying or describing the specimen.
5. Place the secondary container and specimen information in an outer mailing tube or box.
6. Keep the specimens for virus isolation frozen, preferably by placing dry ice around the secondary container in the mailing tube or box (specimens should be frozen initially in a -20 C or -70 C freezer, not in dry ice).
7. Contact CDC or the state health department for advice on labeling and shipping.

EXPOSURE OF LABORATORY PERSONNEL TO SPECIMENS

Laboratory personnel may have handled specimens from the patient during tests carried out early in the illness, before the diagnosis of VHF was considered. Additionally, once the diagnosis is considered, certain routine laboratory tests required for management of the patient may be necessary before the Mobile Laboratory is established (see CLINICAL MANAGEMENT OF PATIENTS WITH SUSPECTED VHF—THE MOBILE LABORATORY). Any person testing laboratory specimens from patients suspected of having VHF should wear surgical gloves and a full-face respirator with an HEPA filter. Care should be taken to minimize use of potentially hazardous procedures, such as ones that produce aerosols, and use of potentially hazardous equipment, such as glass microhematocrit tubes. Laboratory tests should be done in special areas with a Class 2A biological safety cabinet (*11*). All personnel who handled these specimens when not adequately protected should be placed under surveillance (see IDENTIFICATION, SURVEILLANCE, AND MANAGEMENT OF CONTACTS OF PATIENTS WITH VHF). The equipment used to carry out these tests should be decontaminated before being returned to routine use (see DECONTAMINATION PROCEDURES).

CLINICAL MANAGEMENT OF PATIENTS WITH SUSPECTED VHF—THE MOBILE LABORATORY

Case Management

The management of patients severely ill with VHF represents a major challenge to the practitioner of intensive-care medicine. The details of patient management cannot be covered in this document, and no attempt has been made to do so. A few general observations follow; further details may be obtained from the references.

The pathogenesis of VHFs is not clearly understood. Multiple organ systems may be affected by a viral infection that, although not highly inflammatory, is widely disseminated. A hallmark of these diseases is presence of high concentrations of virus in the blood for 2 weeks or longer. Many deaths occur among patients who are admitted during the second week of illness and who may be dehydrated and have low blood pressure. Thus, careful management of fluid and electrolyte balance from the onset of disease is perhaps the most important aid to recovery. Enzyme studies reveal that the liver is regularly affected, although it is doubtful that it is very often damaged sufficiently to cause death. The case-fatality rate in these diseases is higher for persons with overt bleeding than for those without hemorrhage. DIC has been documented only in patients with Marburg disease and CCHF, but its presence may help explain the clinical illness associated with the other hemorrhagic fevers as well. Detection and treatment of bleeding should be given high priority. Other acute problems that may occur include myocarditis and pericarditis, pleural effusion, intrauterine death, and spontaneous abortion.

Therapy is mainly supportive. Immune plasma obtained from persons who have survived the infection in question is frequently used for patients with VHF. However, the efficacy of such treatment has not been established. It is suggested that, if used, immune plasma should be administered early in the illness, preferably in the first week. The simultaneous presence of the virus and its naturally occurring antibodies in the blood of patients during the second week of illness suggests that some of the pathologic effects may be caused by deposition of antigen-antibody complexes. Administering immune plasma under such circumstances may only aggravate the patient's condition. Preliminary studies in Sierra Leone suggest that the antiviral agent ribavirin, if administered during the first week of illness, may be helpful in treating Lassa fever (*12*). This drug has not been studied in connection with the other hemorrhagic fevers.

Mobile Laboratory

Any delay must be avoided in processing routine laboratory specimens necessary for care of the critically ill patient. In the past, however, there has been some reluctance to expose laboratory personnel or equipment to possible contamination with VHF viruses. Therefore, CDC has procured a Vickers Mobile Laboratory*, which can be transported within hours to any hospital in the United States where a person suspected of having VHF is hospitalized (*46*). A qualified laboratory technician experienced in working with VHF materials is available to accompany the laboratory equipment. The Mobile Laboratory includes facilities for performing routine hematologic and blood chemistry studies, coagulation studies, and urinalysis, as well as routine (bacterial) microbiologic cultures. Serologic studies for the agents causing VHF can be done in the Mobile Laboratory, but facilities are not adequate for attempting virus isolation. The laboratory is designed to facilitate the care of the ill patient so that transportation to another medical facility is unnecessary.

The Mobile Laboratory is to be installed in a hospital room with similar features to those of the patient's room and from which air can be exhausted to the outside of the hospital. It is preferable that this room be near the patient's room, have an anteroom or area for dressing, and have shower facilities. The room must have an 8-foot long table or counter with 4 feet of overhead clearance and an additional 8-10 linear feet of counterspace. Eight to ten electrical outlets will be required. Further information concerning the Mobile Laboratory can be obtained by contacting any of the persons listed in the INTRODUCTION.

Autopsy and Handling of the Corpse

Careful consideration should be given to the potential risks and benefits of performing an autopsy on anyone suspected of having died from VHF. If an autopsy must be done, extreme precautions must be taken to prevent dissemination of the virus. Double gloves, cap and gown, waterproof apron and shoe coverings, and full-face respirators equipped with HEPA filters should be worn. Methods should be used to avoid or minimize aerosolization of tissues (e.g., bone should be cut with a hand saw rather than an electric saw). All effluents resulting from the autopsy should be decontaminated before they are washed down the drain, and the autopsy room should be decontaminated after the procedure.

The body should not be embalmed. Rather, the body should be placed in an airtight bag and either cremated or placed in a sealed casket for burial.

DECONTAMINATION PROCEDURES

Conveyances (ambulances, for example), transport and bed isolation units, and hospital rooms can be decontaminated by applying a 0.5% sodium hypochlorite solution or a phenolic disinfectant to all exposed surfaces.

Patient care/management items (such as endoscopes) and laboratory equipment used to process specimens from patients with suspected VHF before the Mobile Laboratory is in place should be decontaminated before being returned to routine use. Surfaces in contact with potentially contaminated liquids, such as flow-through optical and sampling systems, can be decontaminated by flushing with 0.5% sodium hypochlorite. Sufficient solution should be used for the fluid to enter waste-disposal reservoirs in the instruments. Smaller reusable items, such as pipettes, should be immersed in 0.5% sodium hypochlorite and autoclaved. Disposable laboratory materials, such as pipette tips, plastic cuvettes, and excess specimens, should be placed in a rigid plastic container containing 0.5% sodium hypochlorite and autoclaved and discarded or incinerated.

IDENTIFICATION, SURVEILLANCE, AND MANAGEMENT OF CONTACTS OF PATIENTS WITH VHF

A contact is defined as a person who has been exposed to an infected person or his/her secretions, excretions, or tissues in such a way as to be at risk of acquiring the infection. For VHF, this includes anyone who has been associated with an infected person—at any time from onset of fever to 3 weeks later—in any of the following ways:

1. Shared the same residence
2. Had face-to-face contact (within 3 feet) with the patient
3. Had skin or mucous membrane contact and/or a needle stick or other penetrating injury with the patient's secretions, excretions, blood, or tissues

CDC will work with state and local health authorities, as appropriate, to implement surveillance and management of contacts of patients with VHF. Initially, clinicians and hospital authorities should compile a list of individuals to be placed under surveillance, including their addresses and telephone numbers. The usual method of surveillance involves having the individual under surveillance record his/her temperature twice daily and report immediately any temperature of 101 F or greater or any symptoms of illness to the public health officer responsible for surveillance. Any person with a temperature of 101 F or more or other symptoms or signs suggestive of VHF within 3 weeks after exposure should be placed in isolation and treated as a suspected case.

References

1. CDC. Recommendations for initial management of suspected or confirmed cases of Lassa fever. MMWR(suppl) 1980;28:1S-12S.
2. Simpson DIH. Viral haemorrhagic fevers of man. Bull WHO 1978;56:819-32.
3. Frame JD, Baldwin JM Jr, Gocke DJ, et al. Lassa fever, a new virus disease of man from West Africa I. Clinical description and pathological findings. Am J Trop Med Hyg 1970;19:670-6.
4. Leifer E, Gocke DJ, Bourne H. Lassa fever, a new virus disease of man from West Africa II. Report of a laboratory-acquired infection treated with plasma from a person recently recovered from the disease. Am J Trop Med Hyg 1970;19:677-9.
5. CDC. Lassa virus infection—Pennsylvania MMWR 1970;19:123.
6. Monath TP. Lassa fever: review of epidemiology and epizootiology. Bull WHO 1975;52:577-92.
7. Monath TP, Newhouse VF, Kemp GE, et al. Lassa virus isolation from *Mastomys natalensis* rodents during an epidemic in Sierra Leone. Science 1974;185:263-5.
8. Carey DE, Kemp GE, White HA, et al. Lassa fever. Epidemiological aspects of the 1970 epidemic, Jos, Nigeria. Trans R Soc Trop Med Hyg 1972;66:402-8.
9. Fraser DW, Campbell CC, Monath TP, et al. Lassa fever in the Eastern Province of Sierra Leone 1970-1972 I. Epidemiologic studies. Am J Trop Med Hyg 1974;23:1131-9.
10. Knobloch J, McCormick JB, Webb PA, et al. Clinical observations in 42 patients with Lassa fever. Tropenmend Parasitol 1980;31:389-98.
11. CDC; National Institutes of Health. Biosafety in microbiological and biomedical laboratories. Atlanta: CDC; 1983 (in press).
12. CDC. Unpublished data.
13. Zweighaft RM, Fraser DW, Hattwick MAW, et al. Lassa fever: response to an imported case. N Engl J Med 1977;297:803-7.
14. Woodruff AW, Monath TP, Mahmoud AAF, et al. Lassa fever in Britain: an imported case. Br Med J 1973;3:616-7.
15. Gilles HM, Kent JC. Lassa fever: retrospective diagnosis of two patients seen in Great Britain in 1971. Br Med J 1976;2:1173.
16. World Health Organization. Lassa fever. Weekly Epidemiologic Record 1975;50:27
17. World Health Organization. Viral haemorrhagic fever. Weekly Epidemiologic Record 1976;51:261.
18. World Health Organization. Lassa fever surveillance. Weekly Epidemiologic Record 1981;56:47.
19. Emond RTD, Bannister B, Lloyd G, et al. A case of Lassa fever: clinical and virological findings. Br Med J 1982;285:1001-2.
20. World Health Organization. Lassa fever surveillance. Weekly Epidemiologic Record 1982;57:342.
21. World Health Organization. Ebola haemorrhagic fever in Sudan, 1976: Report of a WHO/International Study Team. Bull WHO 1978;56:247-70.
22. World Health Organization. Ebola haemorrhagic fever in Zaire, 1976: Report of an International Commission. Bull WHO 1978;56:271-93.
23. Baron RC, McCormick JB, Zubeir OA. Ebola hemorrhagic fever in Southern Sudan: hospital dissemination and risk of intrafamilial spread. Bull WHO 1983 (in press).
24. Gonzalez JP, McCormick JB, Saluzzo JF, et al. Les fievres hemorragiques Africaines d'origine virale: contribution a leur etude en Republique Centrafricaine. Cahiers Microb Parasitol Ent Med ORSTOM (in press).
25. Johnson BK, Ocheng D, Gitau LG, et al. Viral haemorrhagic fever surveillance in Kenya, 1980-1981. Trop Geogr Med 1983;35:43-7.
26. Kiley MP, Bowen ETW, Eddy GA, et al. Filoviridae: a taxonomic home for Marburg and Ebola viruses? Intervirology 1982;18:24-32.
27. Bowen ETW, Lloyd G, Platt G, et al. Virological studies on a case of Ebola virus infection in man and in monkeys. In Pattyn SR, ed. Ebola virus haemorrhagic fever: proceedings of an international colloquium on Ebola virus infection and other hemorrhagic fevers held in Antwerp, Belgium, 6-8 December, 1977. New York: Elsvier/North-Holland Biomedical Press, 1978:95-102.
28. Richman DD, Cleveland PH, McCormick JB, et al. Antigenic analysis of strains of Ebola virus: identification of two Ebola virus serotypes. J Infect Dis 1983;147:268-71.
29. Emond RTD, Evans B, Bowen ETW, et al. A case of Ebola virus infection. Br Med J 1977;2:541-4.
30. Williams EH. 44 contacts of Ebola virus infection-Salisbury. Public Health The Journal of the Society of Community Medicine. (London) 1979;93:67-75.
31. Martini GA. Marburg virus disease. Clinical syndrome. In: Martini GA, Siegert R, eds. Marburg virus disease. New York: Springer-Verlag, 1971:1-9.

32. Stille W, Bohle E. Clinical course and prognosis of Marburg virus ("green-monkey") disease. In: Martini GA, Siegert R, eds. Marburg virus disease. New York: Springer-Verlag, 1971:10-8.
33. Todorovitch K, Mocitch M, Klasnja R. Clinical picture of two patients infected by the Marburg vervet virus. In: Martine GA, Siegert R, eds. Marburg virus disease. New York: Springer-Verlag, 1971:19-23.
34. Conrad JL, Isaacson M, Smith EB, et al. Epidemiologic investigation of Marburg virus disease, Southern Africa, 1975. Am J Trop Med Hyg 1978;27:1210-5.
35. Gear JSS, Cassel GA, Gear AJ, et al. Outbreak of Marburg virus disease in Johannesburg. Br Med J 1975;4:489-93.
36. Smith DH, Isaacson M, Johnson KM, et al. Marburg virus disease in Kenya. Lancet 1982;1:816-20.
37. World Health Organization. Viral haemorrhagic fever surveillance. Weekly Epidemiologic Record 1982;57:359.
38. Hoogstraal H. The epidemiology of tick-borne Crimean-Congo hemorrhagic fever in Asia, Europe, and Africa. J Med Entomol 1979;15:307-417.
39. Casals J. Antigenic similarity between the virus causing Crimean hemorrhagic fever and Congo virus. Proc Soc Exp Biol Med 1969;131:233-6.
40. Burney MI, Ghafoor A, Saleen M, et al. Nosocomial outbreak of viral hemorrhagic fever caused by Crimean hemorrhagic fever-Congo virus in Pakistan, January, 1976. Am J Trop Med Hyg 1980;29:941-7.
41. Suleiman M, Muscat-Baron JM, Harries JR, et al. Congo/Crimean haemorrhagic fever in Dubai; an outbreak at the Rashid Hospital. Lancet 1980;2:939-41.
42. Al-Tikriti SK, Al-Ani F, Jurji FJ, et al. Congo/Crimean hemorrhagic fever in Iraq. Bull WHO 1981;59:85-90.
43. Goldfarb LG, Chumakov MP, Myskin AA, et al. An epidemiological model of Crimean hemorrhagic fever. Am J Trop Med Hyg 1980;29:260-4.
44. Garner JS, Simmons BP. Centers for Disease Control: Guidelines for isolation precautions in hospitals. Infection Control 1983;4:245-325.
45. CDC. Interstate shipment of etiologic agents. Federal Register 1980;45:48626-9 (DHHS publication no. 42 CFR Part 72).
46. Mitchell SW, McCormick JB. Mobile clinical laboratory manual. Clinical laboratory support for the management of patients suspected of infection with a Class IV agent. Atlanta: CDC, 1982:1-60.

APPENDIX

Suggested List of Essential Supplies and Equipment To Be Kept in Anteroom Adjoining Patient's Room (Excluding Medications)

Equipment for full physical examination
Emergency equipment
Portable X-ray machine
Electrocardiogram machine
Intravenous equipment and supplies
Tourniquets
Dry gauze
Alcohol swabs
Needles and adapters
Syringes
Blood tubes for complete blood count, blood chemistry, and coagulation studies
Containers with Hanks' solution with 1% human serum albumin or 25% rabbit serum albumin for specimens of throat washing and urine
Printed specimen labels with patient's name
Marker pens
Plastic airtight bags, large and small
Large plastic trash bags
0.5% sodium hypochlorite (10% aqueous solution of household bleach), Lysol* solution
Chemical toilet
Urinals
Bed linen (disposable)
Pajamas (disposable)
Thermometers (disposable)
Toiletries, etc. (disposable)

*Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

CENTERS FOR DISEASE CONTROL

June 7, 1985 / Vol. 34 / No. 22

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

Recommendation of the Immunization Practices Advisory Committee (ACIP)

Recommendations for Protection Against Viral Hepatitis

*The following statement updates all previous recommendations on use of immune globulins for protection against viral hepatitis (*MMWR *1981;30:423-35) and use of hepatitis B vaccine and hepatitis B immune globulin for prophylaxis of hepatitis B (*MMWR *1982;31:317-28 and* MMWR *1984;33:285-90).*

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. The third, currently known as non-A, non-B hepatitis, is probably caused by at least two different agents, and lacking specific diagnostic tests, remains a disease diagnosed by exclusion. It is an important form of acute viral hepatitis in adults and currently accounts for most post-transfusion hepatitis in the United States. An epidemic type of non-A, non-B hepatitis, which is probably spread by the fecal-oral route and is different from the types seen in the United States, has been described in parts of Asia and North Africa (*2*).

A fourth type of hepatitis, delta hepatitis, has recently been characterized as an infection dependent on hepatitis B virus. It may occur as a coinfection with acute hepatitis B infection or as superinfection of a hepatitis B carrier (*3*).

HEPATITIS SURVEILLANCE

Approximately 21,500 cases of hepatitis A, 24,300 cases of hepatitis B, 3,500 cases of non-A, non-B hepatitis, and 7,100 cases of hepatitis type unspecified were reported in the United States in 1983. 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 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 professional donors. Only plasma shown to be free of hepatitis B surface antigen (HBsAg) 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 hepatitis B surface antigen (anti-HBs). Tests of IG lots prepared since 1977 indicate that both types of antibody have uniformly been present. Hepatitis B immune globulin (HBIG) is an IG prepared from plasma containing high titers of anti-HBs.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES / PUBLIC HEALTH SERVICE

ACIP: Viral Hepatitis – Continued

Neither IG nor HBIG commercially available in the United States transmits hepatitis or other viral infections. There is no evidence that the causative agent of AIDS (human T-lymphotropic virus type III/lymphadenopathy-associated virus [HTLV-III/LAV]) has been transmitted by IG or HBIG (*4*).

Serious adverse effects from immune globulins administered as recommended have been exceedingly rare. Standard immune globulins are prepared for intramuscular use and should not be given intravenously. Two preparations for intravenous use in immunodeficient and other selected patients have recently become available in the United States but are not recommended for hepatitis prophylaxis. Immune globulins are not contraindicated for pregnant women.

HEPATITIS A

Hepatitis A is caused by the hepatitis A virus (HAV), a 27-nm ribonucleic acid (RNA) agent that is a member of the picornavirus family. The illness caused by HAV characteristically has an abrupt onset with fever, malaise, anorexia, nausea, abdominal discomfort, and jaundice. Severity is related to age. In children, most infections are asymptomatic, and illness is usually not accompanied by jaundice. Most infected adults become symptomatically ill with jaundice. Fatality among reported cases is infrequent (about 0.6%).

Hepatitis A is primarily transmitted by person-to-person contact, generally through fecal contamination. Transmission is facilitated by poor personal hygiene, poor sanitation, and intimate (intrahousehold or sexual) contact. Common-source epidemics from contaminated food and water also occur. Sharing utensils or cigarettes or kissing are not believed to transmit the infection.

The incubation period of hepatitis A is 15-50 days (average 28-30). High concentrations of HAV (10^8 particles/g) are found in stools of infected persons. Fecal virus excretion reaches its highest concentration late in the incubation period and early in the prodromal phase of illness, and diminishes rapidly once jaundice appears. Greatest infectivity is during the 2-week period immediately before the onset of jaundice. Viremia is of short duration; virus has not been found in urine or other body fluids. A chronic carrier state with HAV in blood or feces has not been demonstrated. Transmission of HAV by blood transfusion has occurred but is rare.

The diagnosis of acute hepatitis A is confirmed by finding IgM-class anti-HAV in serum collected during the acute or early convalescent phase of disease. IgG-class anti-HAV, which appears in the convalescent phase of disease and remains detectable in serum thereafter, apparently confers enduring protection against 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 has decreased over the last 15 years, it is still a common infection in older children and young adults. About 38% of reported hepatitis cases in this country are attributable to hepatitis A.

Recommendations for IG prophylaxis of 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 (*5-7*). Its prophylactic value is greatest (80%-90%) when given early in the incubation period and declines thereafter (*7*).

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, incidence of hepatitis A infection in areas visited, and length of stay (*8,9*). In general, travelers to developed areas of western Europe, Japan, and Australia are at no greater risk of infection than in the United States. In contrast, travelers to developing

ACIP: Viral Hepatitis – Continued

countries may be at significant risk of infection. In such areas, the best way to prevent hepatitis A and other enteric diseases is to avoid potentially contaminated water or food. Drinking water (or beverages with ice) of unknown purity and eating uncooked shellfish or uncooked fruits or vegetables that are not peeled (or prepared) by the traveler should be avoided.

IG is recommended for travelers to developing countries if they will be eating in settings of poor or uncertain sanitation (some restaurants or homes) or will be visiting extensively 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 if they anticipate exposure as described above or will be living in rural areas with poor sanitation.

For such travelers, a single dose of IG of 0.02 ml/kg is recommended if travel is for less than 2 months. For prolonged travel, 0.06 ml/kg should be given every 5 months. For persons who require repeated IG prophylaxis, screening for total anti-HAV antibodies before travel may be useful to define susceptibility and eliminate unnecessary doses of IG in those who are immune.

Postexposure prophylaxis. A serologic test for the diagnosis of acute hepatitis A is now widely available. Since only 38% of acute hepatitis cases in the United States result from hepatitis A, serologic confirmation of hepatitis A in the index case is recommended before treatment of contacts. Serologic screening of contacts for anti-HAV before giving IG is not recommended because screening is more costly than IG and would delay its administration.

IG should be given as soon as possible after exposure; giving IG more than 2 weeks after exposure is not indicated.

Specific recommendations for IG prophylaxis of 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 with children in diapers can be important settings for HAV transmission (*10-12*). IG should be administered to all staff and attendees of day-care centers or homes if: (a) one or more hepatitis A cases are recognized among children or employees; 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 whose diapered children attend. In centers not enrolling children in diapers, IG need only be given to classroom contacts of an index case.
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 epidemiologic study clearly shows the existence of a school- or classroom-centered outbreak, IG may be given to those who have close personal 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 in extent 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 emphasize precautions regarding direct contact with potentially infective materials (*13*).

ACIP: Viral Hepatitis – Continued

Outbreaks of hepatitis A among hospital staff occur occasionally, usually in association with an unsuspected index patient who is fecally incontinent. Large outbreaks have occurred among staff and family contacts of infected infants in neonatal intensive-care units. 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 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 in those exposed, since the 2-week period during which IG is effective will have been exceeded.

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

For postexposure IG prophylaxis, a single intramuscular dose of 0.02 ml/kg is recommended.

HEPATITIS B

Hepatitis B virus (HBV) infection is a major cause of acute and chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma worldwide. 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 only 0.1%-0.5% of the population being virus carriers and infection occurring primarily during adulthood. In contrast, HBV infection is highly endemic in China and Southeast Asia, sub-Saharan Africa, most Pacific islands, and the Amazon Basin; in these areas, 5%-15% of the population carry the virus, and most persons acquire infection at birth or during childhood. In other parts of the world, HBV is moderately endemic, and 1%-4% of persons are HBV carriers. Recommendations for prophylaxis of hepatitis B will vary in accordance with local patterns of HBV transmission. The recommendations that follow are intended for use in the United States.

Hepatitis B infection is caused by the HBV, a 42-nm, double-shelled deoxyribonucleic acid (DNA) virus. Several well-defined antigen-antibody systems have been associated with HBV infection (Table 1). HBsAg, formerly called "Australia antigen" or "hepatitis-associated antigen," is found on the surface of the virus and on accompanying 22-nm spherical and tubular forms. HBsAg can be identified in serum 30-60 days after exposure to HBV and persists for variable periods. The various subtypes (adr, adw, ayw, ayr) of HBsAg provide useful epidemiologic markers. Antibody against HBsAg (anti-HBs) develops after a resolved infection and is responsible for long-term immunity. Anti-HBc, the antibody to the core antigen (an internal component of the virus), develops in all HBV infections and persists indefinitely. IgM anti-HBc appears early in infection and persists for 6 or more months; it is a reliable marker of acute or recent HBV infection. The hepatitis B e antigen (HBeAg) is a third antigen, presence of which correlates with HBV replication and high infectivity. Antibody to HBeAg (anti-HBe) develops in most HBV infections and correlates with lower infectivity.

ACIP: Viral Hepatitis – Continued

The onset of acute hepatitis B is generally insidious. Clinical symptoms and signs include various combinations of anorexia, malaise, nausea, vomiting, abdominal pain, and jaundice. Skin rashes, arthralgias, and arthritis can also occur. Overall fatality rates for reported cases generally do not exceed 2%. The incubation period of hepatitis B is long—45-160 days (average 60-120).

TABLE 1. Hepatitis nomenclature

Abbreviation	Term	Comments
	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 anti-HAV	IgM class antibody to HAV	Indicates recent infection with hepatitis A; positive up to 4-6 months after infection.
	Hepatitis B	
HBV	Hepatitis B virus	Etiologic agent of "serum" or "long-incubation" hepatitis; also known as Dane particle.
HBsAg	Hepatitis B surface antigen	Surface antigen(s) of HBV detectable in large 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 HBV vaccine.
Anti-HBe	Antibody to HBeAg	Presence in serum of HBsAg carrier suggests lower titer of HBV.
Anti-HBc	Antibody to HBcAg	Indicates past infection with HBV at some undefined time.
IgM anti-HBc	IgM class antibody to HBcAg	Indicates recent infection with HBV; positive for 4-6 months after infection.
	Delta hepatitis	
δ virus	Delta virus	Etiologic agent of delta hepatitis; may only cause infection in presence of HBV.
δ-Ag	Delta antigen	Detectable in early acute delta infection.
Anti-δ	Antibody to delta antigen	Indicates past or present infection with delta virus.
	Non-A, non-B hepatitis	
NANB	Non-A, non-B hepatitis	Diagnosis of exclusion. At least two candidate viruses; epidemiology parallels that of hepatitis B.
	Epidemic non-A, non-B hepatitis	
Epidemic NANB	Epidemic non-A, non-B hepatitis	Causes large epidemics in Asia, North Africa; fecal-oral or waterborne.
	Immune globulins	
IG	Immune globulin (previously ISG, immune serum globulin, or gamma globulin)	Contains antibodies to HAV, low titer antibodies to HBV.
HBIG	Hepatitis B immune globulin	Contains high titer antibodies to HBV.

ACIP: Viral Hepatitis – Continued

HBV infection in the United States. The estimated lifetime risk of HBV infection in the United States varies from almost 100% for the highest-risk groups to approximately 5% for the population as a whole. An estimated 200,000 persons, primarily young adults, are infected each year. One-quarter become ill with jaundice; more than 10,000 patients require hospitalization; and an average of 250 die of fulminant disease each year. Between 6% and 10% of young adults with HBV infection become carriers. The United States currently contains an estimated pool of 500,000-1,000,000 infectious carriers. Chronic active hepatitis develops in over 25% of carriers and 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. It is estimated that 4,000 persons die from hepatitis B-related cirrhosis each year in this country and that more than 800 die from hepatitis B-related liver cancer.

The role of the HBV carrier is central in the epidemiology of HBV transmission. A carrier is defined as a person who is HBsAg-positive on at least two occasions at least 6 months apart. Although the degree of infectivity is best correlated with HBeAg-positivity, any person positive for HBsAg is potentially infectious. The likelihood of developing the carrier state varies inversely with the age at which infection occurs. During the perinatal period, HBV transmitted from HBeAg-positive mothers results in HBV carriage in up to 90% of infected infants, whereas 6%-10% of acutely infected adults become carriers.

Carriers and persons with acute infection have highest concentrations of HBV in the blood and serous fluids; less is present in other body fluids, such as saliva and semen. Transmission occurs via percutaneous or permucosal routes. Infective blood or body fluids can be introduced by contaminated needles or through sexual contact. Infection can occur in settings of continuous close personal contact, such as in households or among children in institutions for the mentally retarded, presumably via inapparent or unnoticed contact of infectious secretions with skin lesions or mucosal surfaces. Transmission of infection by transfusion of contaminated blood or blood products has been greatly reduced since the advent of routine screening with highly sensitive tests for HBsAg. HBV is not transmitted via the fecal-oral route or by contamination of food or water.

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. Immigrants/refugees and their descendants from areas of high HBV endemicity are at high risk of acquiring HBV infection. Homosexually active men and users of illicit injectable drugs are among the highest-risk groups, acquiring infection soon after adopting these lifestyles (10%-20%/year). Inmates of prisons have high prevalence of HBV markers usually because of prior parenteral drug abuse; actual risk of transmission in prisons is also associated with parenteral drug abuse in prisons. Patients and staff in custodial institutions for the mentally retarded are also at increased risk of having HBV infection. Classroom contacts, particularly teachers or instructors, of some deinstitutionalized carriers may also be at higher risk than the general population. Household contacts and sexual partners of HBV carriers are at increased risk, as are hemodialysis patients and recipients of certain pooled plasma products.

There is increased risk for medical and dental workers and related laboratory and support personnel who have contact with blood. Employment in a hospital without exposure to blood carries no greater risk than that for the general population.

Hepatitis B prophylaxis. Two types of products are available for prophylaxis against hepatitis B. Hepatitis B vaccine, licensed in 1981, provides active immunization against HBV infection, and its use is recommended for both pre- and postexposure prophylaxis. IG products provide temporary, passive protection and are indicated only in certain postexposure settings.

ACIP: Viral Hepatitis — Continued

IG and HBIG. IG and HBIG contain different amounts of anti-HBs. IG is prepared from plasma that is not preselected for anti-HBs content. Since 1977, all lots tested have contained anti-HBs at a titer of at least 1:100 by radioimmunoassay (RIA). HBIG is prepared from plasma preselected for high-titer anti-HBs. In the United States, HBIG has an anti-HBs titer of higher than 1:100,000 by RIA. There is no evidence that the causative agent of AIDS (HTLV-III/LAV) has been transmitted by IG or HBIG (*4*).

Hepatitis B vaccine. Hepatitis B vaccine licensed in the United States is a suspension of inactivated, alum-adsorbed 22-nm surface antigen 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 1:4000 formalin. These treatment steps have been shown to inactivate representatives of all classes of viruses found in human blood, including the causative agent of AIDS (HTLV-III/LAV) (*14*). HB vaccine contains 20 μg/ml of HBsAg protein.

After a series of three intramuscular doses of hepatitis B vaccine, over 90% of healthy adults develop protective antibody (*15,16*). A course of three 10-μg doses induces antibody in virtually all infants and children from birth through 9 years of age. The deltoid (arm) is the recommended site for hepatitis B vaccination in adults; immunogenicity of vaccine in adults is significantly lower when injections are given in the buttock (81%) (*17*). The immunogenicity of the intradermal route has not yet been clearly established.

Field trials of the U.S.-manufactured vaccine have shown 80%-95% efficacy in preventing infection or hepatitis among susceptible persons (*16,18*). Protection against illness is virtually complete for persons who develop adequate antibody levels* after vaccination. The duration of protection and need for booster doses are not yet defined. However, only 10%-15% of per-

*Adequate antibody is 10 or more sample ratio units (SRU) by RIA or positive by enzyme immunoassay.

TABLE 2. Prevalence of hepatitis B serologic markers in various population groups

Population group	Prevalence of serologic markers of HBV infection	
	HBsAg (%)	All markers (%)
High risk		
Immigrants/refugees from areas of high HBV endemicity	13	70-85
Clients in institutions for the mentally retarded	10-20	35-80
Users of illicit parenteral drugs	7	60-80
Homosexually active men	6	35-80
Household contacts of HBV carriers	3-6	30-60
Patients of hemodialysis units	3-10	20-80
Intermediate risk		
Health-care workers— frequent blood contact	1-2	15-30
Prisoners (male)	1-8	10-80
Staff of institutions for the mentally retarded	1	10-25
Low risk		
Health-care workers— no or infrequent blood contact	0.3	3-10
Healthy adults (first-time volunteer blood donors)	0.3	3-5

ACIP: Viral Hepatitis – Continued

sons who develop adequate antibody after three vaccine doses will lose antibody within 4 years, and among those who lose antibody, protection against viremic infection and liver inflammation appears to persist. Immunogenicity and efficacy of the licensed vaccine in hemodialysis patients is much lower than in normal adults; protection may last only as long as adequate antibody levels persist (*19*).

Vaccine usage. Primary vaccination consists of 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 20 μg (1.0 ml) per dose, while children under 10 years should receive 10 μg (0.5 ml) per dose. For patients undergoing hemodialysis and for other immunosuppressed patients, a 40-μg (2.0-ml) dose should be used. Vaccine doses administered at longer intervals provide equally satisfactory protection, but optimal protection is not conferred until after the third dose. Hepatitis B vaccine should only be given in the deltoid muscle in adults and children or in the anterolateral thigh muscle in infants and neonates. Since hepatitis B vaccine is an inactivated (noninfective) product, it is presumed that there will be no interference with other simultaneously administered vaccines.

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

Vaccine storage. Vaccine should be stored at 2 C-8 C (36 F-46 F) but not frozen. *Freezing destroys the potency of the vaccine.*

Side effects and adverse reactions. The most common side effect observed in prevaccination trials was soreness at the injection site. Among an estimated 750,000 vaccinees, approximately 100 episodes of severe illness have been reported after receipt of vaccine. These have included arthralgias, neurologic reactions (such as Guillain-Barré syndrome), and other illnesses. The rate of Guillain-Barré syndrome following HB vaccine does not appear to be significantly increased above that observed in normal adults. Such temporally associated illnesses are not considered to be etiologically related to hepatitis B vaccine.

Effect of vaccination on carriers and immune persons. The vaccine produces neither therapeutic nor adverse effects in HBV carriers (*20*). 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 from HBIG or IG administration or from the transplacental route, will not interfere with active immunization (*21*).

Prevaccination serologic screening for susceptibility. The decision to screen potential vaccine recipients for prior infection depends on three variables: (1) the cost of vaccination; (2) the cost of testing for susceptibility; and (3) the expected prevalence of immune individuals in the group. Figure 1 shows the relative cost-effectiveness of screening, given different costs of screening tests and the expected prevalence of immunity. In constructing the figure, the assumption was made that the cost of three doses of vaccine is $100 and that there are additional costs for administration. For any combination of screening costs and immunity to hepatitis, the cost-effectiveness can be estimated. For example, if the expected prevalence of serologic markers for HBV is over 20%, screening is cost-effective if costs of screening are no greater than $30 per person. If the expected prevalence of markers is less than 8%, and if the costs of screening are greater than $10 per person, vaccination without screening is cost-effective.

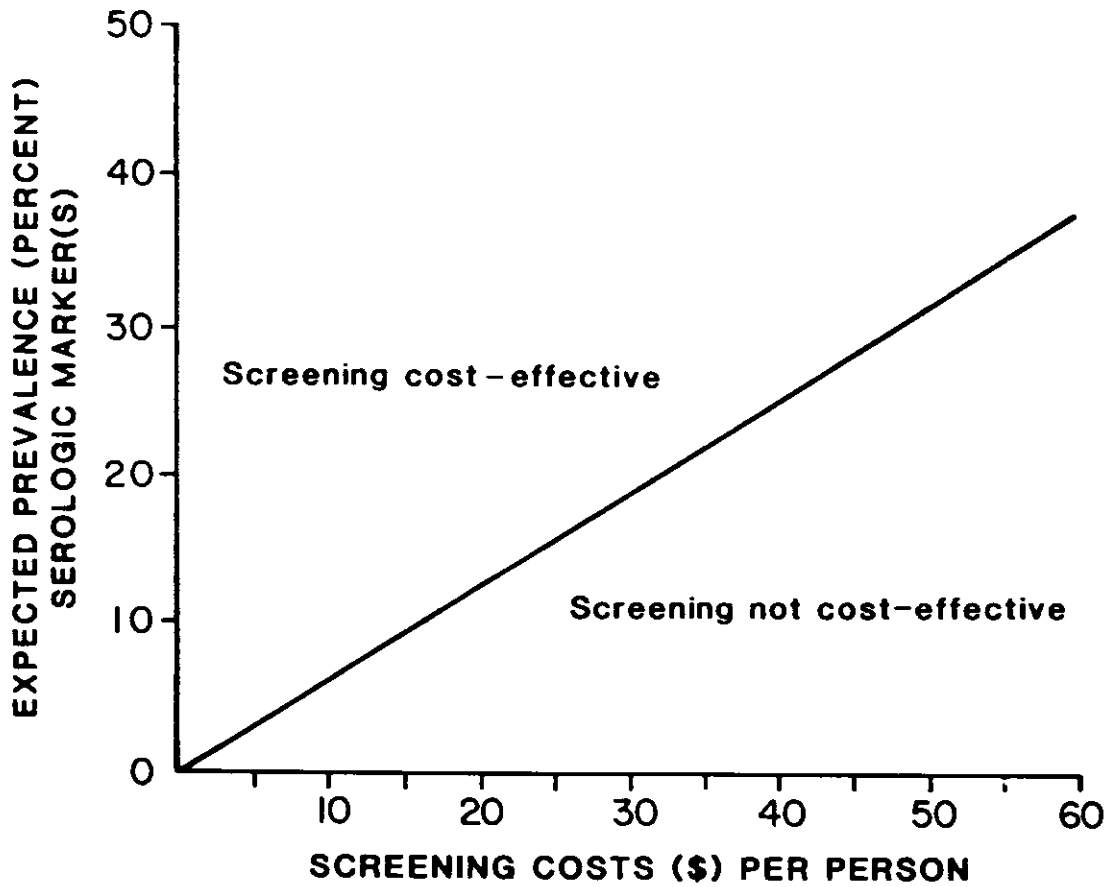
ACIP: Viral Hepatitis – Continued

Screening in groups with the highest risk of HBV infection (Table 2) will be cost-effective unless testing costs are extremely high. For groups at intermediate risk, cost-effectiveness of screening may be marginal, and vaccination programs may or may not utilize screening. For groups with a low expected prevalence of HBV serologic markers, such as health professionals in their training years, screening will not be cost-effective.

For routine screening, only one antibody test, either anti-HBc or anti-HBs, need be used. Anti-HBc will identify all previously infected persons, both carriers and noncarriers, but will not discriminate between members of the two groups. Anti-HBs will identify those previously infected, except carriers. For groups expected to have carrier rates of under 2%, such as health-care workers, neither test has a particular advantage. For groups with higher carrier rates, anti-HBc may be preferred to avoid unnecessary vaccination of carriers. If the RIA anti-HBs test is used for screening, a minimum of 10 RIA sample ratio units should be used to designate immunity (2.1 is the usual designation of a positive test). If enzyme immunoassay (EIA) is used, the manufacturers' recommended positive is appropriate.

Serologic confirmation of postvaccination immunity and revaccination of nonresponders. When given in the deltoid, hepatitis B vaccine produces protective antibody (anti-HBs) in more than 90% of healthy persons. Testing for immunity following vaccination is not recommended routinely but is advised for persons whose subsequent management depends on

FIGURE 1. Cost-effectiveness of prevaccination screening of hepatitis B virus vaccine candidates*



*See text for assumptions.

ACIP: Viral Hepatitis – Continued

knowing their immune status, such as dialysis patients and staff, and for persons in whom a suboptimal response may be anticipated, such as those who have received vaccine in the buttock.

Revaccination of persons who do not respond to primary series (nonresponders) produces adequate antibody in only one-third when the primary vaccination has been given in the deltoid. Therefore, revaccination of nonresponders to deltoid injection is not recommended routinely. For persons who did not respond to a primary vaccine series given in the buttock, preliminary data from two small studies suggest that revaccination in the arm induces adequate antibody in over 75%. Revaccination should be strongly considered for such persons.

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

1. *Health-care workers.* The risk of health-care workers acquiring HBV infection depends on the frequency of exposure to blood or blood products and on the frequency of needlesticks. These risks vary during the training and working career of each individual but are often highest during the professional training period. For this reason, it is recommended that vaccination be completed during training in schools of medicine, dentistry, nursing, laboratory technology, and other allied health professions.

   The risk of HBV infection for hospital personnel can vary both among hospitals and within hospitals. In developing specific immunization strategies, hospitals should use available published data about the risk of infection (*22-24*) and may wish to evaluate their own clinical and institutional experience with hepatitis B. Studies in urban centers have indicated that occupational groups with frequent exposure to blood and/or needles have the highest risk of acquiring HBV infection, including (but not limited to) the following groups: medical technologists, operating room staff, phlebotomists and intravenous therapy nurses, surgeons and pathologists, and oncology and dialysis unit staff. Groups shown to be at increased risk in some hospitals include: emergency room staff, nursing personnel, and staff physicians.

   Other health-care workers based outside hospitals who have frequent contact with blood or blood products are also at increased risk of acquiring HBV infection. These include (but are not limited to): dental professionals (dentists, oral surgeons, dental hygienists), laboratory and blood bank technicians, dialysis center staff, emergency medical technicians, and morticians.
2. *Clients and staff of institutions for the mentally retarded.* Susceptible clients and staff who work closely with clients of institutions for the mentally retarded should be vaccinated. Risks for staff are comparable to those for health-care personnel in other high-risk environments. However, the risk in institutional environments is associated, not only with blood exposure, but also with 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.
3. *Hemodialysis patients.* Numerous studies have established the high risk of HBV transmission in hemodialysis units. Although recent data have shown not only a decrease in the rate of HBV infection in hemodialysis units but also a lower vaccine efficacy in these patients, vaccination is recommended for susceptible patients. Environmental control measures and regular serologic screening (based on immune status) of patients should be maintained.
4. *Homosexually active men.* Susceptible homosexually active men should be vaccinated regardless of their ages or duration of their homosexual practices. It is important to

ACIP: Viral Hepatitis – Continued

vaccinate persons as soon as possible after their homosexual activity begins. Homosexually active women are not at increased risk of sexually transmitted HBV infection.

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 use begins.
6. *Recipients of certain blood products.* Patients with clotting disorders who receive clotting factor concentrates have an elevated risk of acquiring HBV infection. Vaccination is recommended for these persons and should be initiated at the time their specific clotting disorder is identified. Screening 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 acquiring 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, or other screening programs, they should be notified of their status and their susceptible household contacts vaccinated.

   Families accepting orphans or unaccompanied minors from countries of high HBV endemicity should have the child screened for HBsAg, and if positive, family members should be vaccinated.
8. *Other contacts of HBV carriers.* Persons in casual contact with carriers at schools, offices, etc., are at minimal risk of acquiring HBV infection, and vaccine is not routinely recommended for them. However, classroom contacts of deinstitutionalized mentally retarded HBV carriers who behave aggressively or have special medical problems that increase the risk of exposure to their blood or serous secretions may be at risk. In such situations, vaccine may be offered to classroom contacts.
9. *Special high-risk populations.* Some American populations, such as Alaskan Eskimos, native Pacific islanders, and immigrants and refugees from areas with highly endemic disease (particularly eastern Asia and sub-Saharan Africa) have high HBV infection rates. Depending on specific epidemiologic and public health considerations, more extensive vaccination programs should be considered.
10. *Inmates of long-term correctional facilities.* The prison environment may provide a favorable setting for the transmission of HBV because of the frequent use of illicit injectable drugs and homosexual practices. Moreover, it provides an access point for vaccination of parenteral drug abusers. Prison officials should consider undertaking screening and vaccination programs directed at those who abuse drugs before or while in prison.
11. *Heterosexually active persons.* Heterosexually active persons with multiple sexual partners are at increased risk of acquiring HBV infection; risk increases with increasing sexual activity. Vaccination should be considered for persons who present for treatment of sexually transmitted diseases and who have histories of sexual activity with multiple partners.
12. *International travelers.* Vaccination should be considered for persons who plan to reside 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. Hepatitis B vaccination of travelers ideally should begin 6 months before travel in order to complete the full vaccine series; however, a partial series will offer some protection against HBV infection.

ACIP: Viral Hepatitis – Continued

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; or sexual exposure to an HBsAg-positive person.

Recent studies have established the relative efficacies of immune globulins and/or hepatitis B vaccine in various exposure situations. For perinatal exposure to an HBsAg-positive, HBeAg-positive mother, a regimen combining one dose of HBIG at birth with the hepatitis B vaccine series started soon after birth is 85%-90% effective in preventing development of the HBV carrier state (*25,27*). Regimens involving either multiple doses of HBIG alone, or the vaccine series alone, have 70%-75% efficacy, while a single dose of HBIG alone has only 50% efficacy (*28*).

For accidental percutaneous exposure or sexual exposure, only regimens including HBIG and/or IG have been studied. A regimen of two HBIG doses, one given after exposure and one a month later, is about 75% effective in preventing hepatitis B following percutaneous exposure; a single dose of HBIG has similar efficacy when used following sexual exposure (*29-31*).

(Continued on page 329)

ACIP: Viral Hepatitis – Continued

IG may have some effect in preventing clinical hepatitis B following percutaneous exposures and can be considered as an alternative to HBIG when it is not possible to obtain HBIG.

Recommendations on postexposure prophylaxis are based on the efficacy data discussed above and on the likelihood of future HBV exposure of the person requiring treatment. In perinatal exposure and percutaneous exposure of high-risk health-care personnel, 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. One of the most efficient modes of HBV transmission is from mother to infant during birth. If the mother is positive for both HBsAg and HBeAg, about 70%-90% of infants will become infected, and up to 90% of these infected infants will become HBV carriers. If the HBsAg-positive carrier mother is HBeAg-negative, or if anti-HBe is present, transmission occurs less frequently and rarely leads to the HBV carrier state. However, severe acute disease, including fatal fulminant hepatitis in the neonate, has been reported (*32,33*). Prophylaxis of infants from all HBsAg-positive mothers is recommended, regardless of the mother's HBeAg or anti-HBe status.

The efficacy of a combination of HBIG plus the hepatitis B vaccine series has been confirmed in recent studies. Although the following regimen is recommended (Table 3), other schedules have also been effective (*25-27,34*). The major consideration for all these regimens is the need to give HBIG as soon as possible after delivery.

HBIG (0.5 ml [10 μg]) should be administered intramuscularly after physiologic stabilization of the infant and preferably within 12 hours of birth. Hepatitis B vaccine should be administered intramuscularly in three doses of 0.5 ml (10 μg) each. The first dose should be given concurrently with HBIG but at a different site. If vaccine is not available at birth, the first vaccine dose may be given within 7 days of birth. The second and third doses should be given 1 month and 6 months, respectively, after the first. Testing for HBsAg and anti-HBs is recommended at 12-15 months to monitor the final success or failure of therapy. If HBsAg is not detectable, and anti-HBs is present, the child has been protected. Testing for anti-HBc is not useful, since maternal anti-HBc may persist for more than 1 year; the utility of testing for IgM anti-HBc is currently being evaluated. HBIG administered at birth should not interfere with oral polio and diphtheria-tetanus-pertussis vaccines administered at 2 months of age.

Maternal screening. Since efficacy of the treatment regimen depends on administering HBIG on the day of birth, it is vital that HBsAg-positive mothers be identified before delivery. Mothers belonging to groups known to be at high risk of acquiring HBV infection (Table 4)

TABLE 3. Hepatitis B virus postexposure recommendations

	HBIG		Vaccine	
Exposure	Dose	Recommended timing	Dose	Recommended timing
Perinatal	0.5 ml IM	Within 12 hours	0.5 ml (10 μg) IM of birth	Within 12 hours of birth* repeat at 1 and 6 months
Sexual	0.06 ml/kg IM	Single dose within 14 days of sexual contact	†	—

*The first dose can be given the same time as the HBIG dose but at a different site.

†Vaccine is recommended for homosexual men and for regular sexual contacts of HBV carriers and is optional in initial treatment of heterosexual contacts of persons with acute HBV.

ACIP: Viral Hepatitis – Continued

should be tested routinely for HBsAg during a prenatal visit. If a mother belonging to a high-risk group has not been screened prenatally, HBsAg screening should be done at the time of delivery, or as soon as possible thereafter, and the infant treated as above if the mother is HBsAg-positive. If the mother is identified as HBsAg-positive more than 1 month after giving birth, the infant should be screened for HBsAg, and if negative, treated with hepatitis B vaccine and HBIG.

The appropriate obstetric and pediatric staff should be notified directly of HBsAg-positive mothers, so the staff may take appropriate precautions to protect themselves and other patients from infectious material, blood, and secretions, and so the neonate may receive therapy without delay after birth.

Acute exposure to blood that contains (or might contain) HBsAg. For accidental percutaneous or permucosal exposure to blood that is known to contain or might contain HBsAg, the decision to provide prophylaxis must take into account several factors: (1) the hepatitis B vaccination status of the exposed person; (2) whether the source of blood is known or unknown; and (3) whether the HBsAg status of the source is known or unknown. Such exposures usually occur in persons who are candidates for hepatitis B vaccine; for any exposure in a person not previously vaccinated, hepatitis B vaccination is recommended.

The following outline and table summarize prophylaxis for percutaneous (needlestick or bite), ocular, or mucous-membrane exposure to blood according to the source of exposure and vaccination status of the exposed person (Table 5). For greatest effectiveness, passive prophylaxis with HBIG (or IG) should be given as soon as possible after exposure (its value beyond 7 days of exposure is unclear).

1. *Exposed person not previously vaccinated.* Hepatitis B vaccination should be considered the treatment of choice. Depending on the source of the exposure, HBsAg testing of the source and additional prophylaxis of the exposed person may be warranted (see below). Screening the exposed person for immunity should be considered if such screening is cost-effective (as discussed in preexposure prophylaxis) and if this will not delay treatment beyond 7 days.
   a. *Source known HBsAg-positive.* 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 (20 μg) should be given intramuscularly at a separate site within 7 days of exposure, and the second and third doses given 1 month and 6 months later (Table 5).† If HBIG cannot be obtained, IG in an equivalent dosage (0.06 ml/kg) may provide some benefit.

†For persons who are not given hepatitis B vaccine, a second dose of HBIG should be given 1 month after the first dose.

TABLE 4. Women for whom prenatal HBsAg screening is recommended

1. Women of Asian, Pacific island, or Alaskan Eskimo descent, whether immigrant or U.S.-born.
2. Women born in Haiti or sub-Saharan Africa.
3. Women with histories of:
   a. Acute or chronic liver disease.
   b. Work or treatment in a hemodialysis unit.
   c. Work or residence in an institution for the mentally retarded.
   d. Rejection as a blood donor.
   e. Blood transfusion on repeated occasions.
   f. Frequent occupational exposure to blood in medico-dental settings.
   g. Household contact with an HBV carrier or hemodialysis patient.
   h. Multiple episodes of venereal diseases.
   i. Percutaneous use of illicit drugs.

ACIP: Viral Hepatitis – Continued

b. *Source known, HBsAg status unknown.* The following guidelines are suggested based on the relative probability that the source is HBsAg-positive and on the consequent risk of HBV transmission:

(1) *High risk that the source is HBsAg-positive, such as patients with a high risk of HBV carriage (Table 2) or patients with acute or chronic liver disease (serologically undiagnosed).* The exposed person should be given the first dose of hepatitis B vaccine (20 μg) within 1 week of exposure and vaccination completed as recommended. The source person should be tested for HBsAg. If positive, the exposed person should be given HBIG (0.06 ml/kg) if within 7 days of exposure.

(2) *Low risk that the source is positive for HBsAg.* The exposed person should be given the first dose of hepatitis B vaccine (20 μg) within 1 week of exposure and vaccination completed as recommended. Testing of the source person is not necessary.

c. *Source unknown.* The exposed person should be given the first dose of hepatitis B vaccine (20 μg) within 7 days of exposure and vaccination completed as recommended.

2. *Exposed person previously vaccinated against hepatitis B.* For percutaneous exposures to blood in persons who have previously received one or more doses of hepatitis B vaccine, the decision to provide additional prophylaxis will depend on the source of exposure and on whether the vaccinated person has developed anti-HBs following vaccination.

a. *Source known HBsAg-positive.* The exposed person should be tested for anti-HBs unless he/she has been tested within the last 12 months. If the exposed person has adequate[§] antibody, no additional treatment is indicated.

[§]Adequate antibody is 10 SRU or more by RIA or positive by EIA.

TABLE 5. Recommendations for hepatitis B prophylaxis following percutaneous exposure

Source	Exposed person	
	Unvaccinated	Vaccinated
HBsAg-positive	1. HBIG x 1 immediately* 2. Initiate HB vaccine† series.	1. Test exposed person for anti-HBs.§ 2. If inadequate antibody,¶ HBIG (x1) immediately plus HB vaccine booster dose.
Known source		
High-risk HBsAg-positive	1. Initiate HB vaccine series 2. Test source for HBsAg. If positive, HBIG x 1.	1. Test source for HBsAg only if exposed is vaccine nonresponder; if source is HBsAg-positive, give HBIG x 1 immediately plus HB vaccine booster dose
Low-risk HBsAg-positive	Initiate HB vaccine series.	Nothing required.
Unknown source	Initiate HB vaccine series.	Nothing required.

*HBIG dose 0.06 ml/kg IM.

†HB vaccine dose 20 μg IM for adults; 10 μg IM for infants or children under 10 years of age. First dose within 1 week; second and third doses, 1 and 6 months later.

§ See text for details.

¶Less than 10 SRU by RIA, negative by EIA.

ACIP: Viral Hepatitis – Continued

(1) If the exposed person has not completed vaccination and has inadequate levels of antibody, one dose of HBIG (0.06 ml/kg) should be given immediately and vaccination completed as scheduled.

(2) If the exposed person has inadequate antibody on testing or has previously not responded to vaccine, one dose of HBIG should be given immediately and a booster dose of vaccine (1 ml or 20 μg) given at a different site.

(3) If the exposed person shows inadequate antibody on testing but is known to have had adequate antibody in the past, a booster dose of hepatitis B vaccine (1 ml or 20 μg) should be given.

b. *Source known, HBsAg status unknown.*

(1) *High risk that the source is HBsAg-positive.* Additional prophylaxis is necessary only if the exposed person is a known vaccine nonresponder. In this circumstance, the source should be tested for HBsAg and, if positive, the exposed person treated with one dose of HBIG (0.06 ml/kg) immediately and a booster dose of vaccine (1 ml or 20 μg) at a different site. In other circumstances, screening of the source for HBsAg and the exposed person for anti-HBs is not routinely recommended, because the actual risk of HBV infection is very low (less than 1 per 1,000).[¶]

(2) *Low risk that the source is HBsAg-positive.* The risk of HBV infection is minimal. Neither testing of the source for HBsAg, nor testing of the exposed person for anti-HBs, is recommended.

c. *Source unknown.* The risk of HBV infection is minimal. No treatment is indicated.

Sexual contacts of persons with acute HBV infection. Sexual contacts 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 (*31*). 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. Prescreening sexual partners for susceptibility before treatment 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 group.

A single dose of HBIG (0.06 ml/kg) is recommended for susceptible individuals who have had sexual contact with an HBsAg-positive person, if HBIG can be given within 14 days of the last sexual contact, and for persons who will continue to have sexual contact with an individual with acute hepatitis B before loss of HBsAg in that individual. In exposures between heterosexuals, hepatitis B vaccination may be initiated at the same time as HBIG prophylaxis; such treatment may improve efficacy of postexposure treatment. However, since 90% of persons with acute HBV infection become HBsAg-negative within 15 weeks of diagnosis, the potential for repeated exposure to HBV is limited. Hepatitis B vaccine is, therefore, optional in initial treatment for such exposures. If vaccine is not given, a second dose of HBIG should be given if the index patient remains HBsAg-positive for 3 months after detection. If the index patient is a known carrier or remains positive for 6 months, hepatitis B vaccine should be offered to regular sexual contacts. For exposures among homosexual men, the hepatitis B vaccine series should be initiated at the time HBIG is given, since hepatitis B vaccine is recommended for all susceptible homosexual men. Additional doses of HBIG are unnecessary if vaccine is given. IG

[¶]Estimated by multiplying the risk of vaccine nonresponse in the exposed person (.10) by the risk of the needle source being HBsAg-positive (.05) by the risk of HBV infection in a susceptible person having an HBsAg-positive needle-stick injury (.20).

ACIP: Viral Hepatitis – Continued

is an alternative to HBIG when it is not possible to obtain HBIG.

Household contacts of persons with 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 case, such as by sharing toothbrushes or razors. Such exposures should be treated similarly to sexual exposures. If the index patient becomes a hepatitis B carrier, all household contacts should be given hepatitis B vaccine.

DELTA HEPATITIS

The delta virus (also known as hepatitis D virus [HDV] by some investigators) is a defective virus that may only cause infection in the presence of active HBV infection. The delta virus has been characterized as a particle of 35-37 nm in size, consisting of RNA (mw 500,000) as genetic material and an internal protein antigen (delta-antigen), coated with HBsAg as the surface protein (*3*). Infection may occur as either coinfection with hepatitis B or superinfection of a hepatitis B carrier, each of which usually cause an episode of acute hepatitis. Coinfection usually resolves, while superinfection frequently causes chronic delta infection and chronic active hepatitis. Both types of infection may cause fulminant hepatitis.

Delta infection may be diagnosed by detection of delta-antigen in serum during early infection and by the appearance of delta antibody during or after infection. Routes of delta transmission appear to be similar to those of hepatitis B. In the United States, delta infection occurs most commonly among persons at high risk of acquiring HBV infection, such as drug addicts and hemophilia patients.

A test for detection of delta antibody is expected to be commercially available soon. Other tests (delta antigen, IgM anti-delta) are available only in research laboratories.

Since the delta virus is dependent on hepatitis B for replication, prevention of hepatitis B infection, either preexposure or postexposure, will suffice to prevent delta infection in a person susceptible to hepatitis B. Known episodes of perinatal, sexual, or percutaneous exposure to sera or persons positive for both HBV and delta virus should be treated exactly as such exposures to hepatitis B alone.

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

NON-A, NON-B HEPATITIS

United States. Non-A, non-B hepatitis that presently occurs in the United States has epidemiologic characteristics similar to those of hepatitis B, occurring most commonly following blood transfusion and parenteral drug abuse. Multiple episodes of non-A, non-B hepatitis have been observed in the same individuals and may be due to different agents. Chronic hepatitis following acute non-A, non-B hepatitis infection varies in frequency from 20% to 70%. Experimental studies in chimpanzees have confirmed the existence of a carrier state, which may be present in up to 8% of the population.

Although several studies have attempted to assess the value of prophylaxis with IG against non-A, non-B hepatitis, the results have been equivocal, and no specific recommendations can be made (*35,36*). However, for persons with percutaneous exposure to blood from a patient with non-A, non-B hepatitis, it may be reasonable to administer IG (0.06 ml/kg) as soon as possible after exposure.

Epidemic (fecal-oral) non-A, non-B hepatitis. In recent years, epidemics of non-A, non-B hepatitis spread by water or close personal contact have been reported from several areas of Southeast Asia (Indian subcontinent, Burma) and north Africa (*2*). Such epidemics generally

ACIP: Viral Hepatitis — Continued

affect adults and cause unusually high mortality in pregnant women. The disease has been transmitted to experimental animals, and candidate viruses have been identified; however, no serologic tests have yet been developed (*37*).

Epidemic non-A, non-B hepatitis has not been recognized in the United States or western Europe, and it is unknown whether the causative agent is present in these areas.

Travelers to areas having epidemic non-A, non-B hepatitis may be at some risk of acquiring this disease by close contact or by contaminated food or water. The value of IG in preventing this infection is unknown. The best prevention of infection is to avoid potentially contaminated food or water, as with hepatitis A and other enteric infections.

References

1. Francis DP, Maynard JE. The transmission and outcome of hepatitis A, B, and non-A, non-B: a review. Epidemiol Rev 1979;1:17-31.
2. Maynard JE. Epidemic non-A, non-B hepatitis. Seminars in Liver Disease 1984;4:336-9.
3. Rizzetto M. The delta agent. Hepatology 1983;3:729-37.
4. CDC. Provisional public health service inter-agency recommendations for screening donated blood and plasma for antibody to the virus causing acquired immunodeficiency syndrome. MMWR 1985;34:1-5.
5. Kluge T. Gamma-globulin in the prevention of viral hepatitis. A study on the effect of medium-size doses. Acta Med Scand 1963;174:469-77.
6. Stokes J Jr, Neefe JR. The prevention and attenuation of infectious hepatitis by gamma globulin. Preliminary note. JAMA 1945;127:144-5.
7. Mosley JW, Reisler DM, Brachott D, Roth D, Weiser J. Comparison of two lots of immune serum globulin for prophylaxis of infectious hepatitis. Am J Epidemiol 1968;87:539-50.
8. Woodson RD, Cahill KM. Viral hepatitis abroad. Incidence in Catholic missionaries. JAMA 1972; 219:1191-3.
9. Woodson RD, Clinton JJ. Hepatitis prophylaxis abroad. Effectiveness of immune serum globulin in protecting Peace Corps volunteers. JAMA 1969;209:1053-8.
10. Storch G, McFarland LM, Kelso K, Heilman CJ, Caraway CT. Viral hepatitis associated with day-care centers. JAMA 1979;242:1514-8.
11. Hadler SC, Webster HM, Erben JJ, Swanson JE, Maynard JE. Hepatitis A in day-care centers. A community-wide assessment. N Engl J Med 1980;302:1222-7.
12. Hadler SC, Erben JJ, Matthews D, Starko K, Francis DP, Maynard JE. Effect of immunoglobulin on hepatitis A in day-care centers. JAMA 1983;249:48-53.
13. Favero MS, Maynard JE, Leger RT, Graham DR, Dixon RE. Guidelines for the care of patients hospitalized with viral hepatitis. Ann Intern Med 1979;91:872-6.
14. ACIP. Hepatitis B vaccine: evidence confirming lack of AIDS transmission. MMWR 1984;33:685-7.
15. Krugman S, Holley HP Jr, Davidson M, Simberkoff MS, Matsaniotis N. Immunogenic effect of inactivated hepatitis B vaccine: comparison of 20 microgram and 40 microgram doses. J Med Virol 1981;8:119-21.
16. Szmuness W, Stevens CE, Harley EJ, et al. Hepatitis B vaccine: demonstration of efficacy in a controlled clinical trial in a high-risk population in the United States. N Engl J Med 1980;303:833-41.
17. CDC. Suboptimal response to hepatitis B vaccine given by injection into the buttock. MMWR 1985;34:105-13.
18. Francis DP, Hadler SC, Thompson SE, et al. The prevention of hepatitis B with vaccine. Report of the Centers for Disease Control multi-center efficacy trial among homosexual men. Ann Intern Med 1982;97:362-6.
19. Stevens CE, Alter HJ, Taylor PE, Zang EA, Harley EJ, Szmuness W. Hepatitis B vaccine in patients receiving hemodialysis. Immunogenicity and efficacy. N Engl J Med 1984;311:496-501.
20. Dienstag JL, Stevens CE, Bhan AK, Szmuness W. Hepatitis B vaccine administered to chronic carriers of hepatitis B surface antigen. Ann Intern Med 1982;96:575-9.
21. Szmuness W, Stevens CE, Oleszko WR, Goodman A. Passive-active immunisation against hepatitis B: immunogenicity studies in adult Americans. Lancet 1981;1:575-7.
22. Pattison CP, Maynard JE, Berquist KR, Webster HM. Epidemiology of hepatitis B in hospital personnel. Am J Epidemiol 1975;101:59-64.
23. Dienstag JL, Ryan DM. Occupational exposure to hepatitis B virus in hospital personnel: infection or immunization? Am J Epidemiol 1982;115:26-39.

ACIP: Viral Hepatitis – Continued

24. Maynard JE. Viral hepatitis as an occupational hazard in the health care profession. In: Vyas GN, Cohen SN, Schmid R, eds. Viral hepatitis. Philadelphia: Franklin Institute Press, 1978:321-31.
25. Beasley RP, Hwang LY, Lee GC, et al. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. Lancet 1983;2:1099-102.
26. Wong VCW, Ip HMH, Reesink HW, et al. Prevention of the HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HBeAg by administration of hepatitis-B vaccine and hepatitis-B immunoglobulin: double-blind randomised placebo-controlled study. Lancet 1984; 1:921-6.
27. Stevens CE, Toy PT, Tong MJ, et al. Perinatal hepatitis B virus transmission in the United States. Prevention by passive-active immunization. JAMA 1985;253:1740-5.
28. Beasley RP, Hwang LY, Stevens CE, et al. Efficacy of hepatitis B immune globulin for prevention of perinatal transmission of the hepatitis B virus carrier state: final report of a randomized double-blind, placebo-controlled trial. Hepatology 1983:3:135-41.
29. Seeff LB, Wright EC, Zimmerman HJ, et al. Type B hepatitis after needle-stick exposure: prevention with hepatitis B immune globulin. Final report of the Veterans Administration Cooperative Study. Ann Intern Med 1978;88:285-93.
30. Grady GF, Lee VA, Prince AM, et al. Hepatitis B immune globulin for accidental exposures among medical personnel: final report of a multicenter controlled trial. J Infect Dis 1978;138:625-38.
31. Redeker AG, Mosley JW, Gocke DJ, McKee AP, Pollack W. Hepatitis B immune globulin as a prophylactic measure for spouses exposed to acute type B hepatitis. N Engl J Med 1975;293:1055-9.
32. Sinatra FR, Shah P, Weissman JY, Thomas DW, Merritt RJ, Tong MJ. Perinatal transmitted acute icteric hepatitis B in infants born to hepatitis B surface antigen-positive and anti-hepatitis Be-positive carrier mothers. Pediatrics 1982;70:557-9.
33. Delaplane D, Yogev R, Crussi F, Shulman ST. Fatal hepatitis B in early infancy: the importance of identifying HBsAg-positive pregnant women and providing immunoprophylaxis to their newborns. Pediatrics 1983;72:176-80.
34. Seeff LB, Koff RS. Passive and active immunoprophylaxis of hepatitis B. Gastroenterology 1984;86:958-81.
35. Seeff LB, Zimmerman JH, Wright EL, et al. A randomized, double-blind controlled trial of the efficacy of immune serum globulin for the prevention of post-transfusion hepatitis. A Veterans Administration cooperative study. Gastroenterology 1977;72:111-21.
36. Knodell RG, Conrad ME, Ginsburg AL, Bell CJ, Flannery EP. Efficacy of prophylactic gammaglobulin in preventing non-A, non-B post-transfusion hepatitis. Lancet 1976;1:557-61.
37. Kane MA, Bradley DW, Shrestha SM, et al. Epidemic non-A, non-B hepatitis in Nepal. Recovery of a possible etiologic agent and transmission studies in marmosets. JAMA 1984;252:3140-5.