The prevention of hepatitis

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The identification and characterisation of the hepatitis viruses A, B, C, D and E has allowed greater insight into their diagnosis, prevalence and modes of transmission. The clinical, pathological and serological features of each of these viruses have been dealt with elsewhere in this issue of the *SAMJ*, as have general and specific measures required for the prevention and future elimination of the diseases they cause. A recent consensus statement defined the problem posed by the hepatitis viruses in South Africa and highlighted the measures necessary to manage this effectively.[1] This article will concentrate on measures designed to convey passive or active immunity to hepatitis A and B. However, the importance of general measures for the upliftment of underprivileged communities must constantly be borne in mind since these play a vital role in reducing infection, morbidity and mortality due to the hepatitis viruses.

Hepatitis A virus (HAV)

General measures

Hepatitis A infection is spread by the faecal-oral route. In developing countries 100% of the population have antibodies against hepatitis A by age 20, whereas in developed countries only 30 - 50% of the adult population have evidence of previous exposure to the virus.[2] The higher incidence in developing countries is largely thought to be due to poor housing, lack of clean water and inadequate sewerage systems, and measures aimed at addressing these inadequacies could be expected to reduce infection by at least 50%. Travellers from developed countries should avoid local drinking water, ice cubes, shellfish, salads and uncooked food when visiting hyperendemic areas.[3]

Pre-exposure prophylaxis

The morbidity and mortality of hepatitis A is age-related. In black South Africans infection with hepatitis A usually occurs in childhood and is most often subclinical and anicteric. In white South Africans there is less infection in childhood and more infection in older children and adults,[4] who often develop full-blown, icteric disease which occasionally progresses to acute liver failure.

Passive immunisation

A major indication for pre-exposure passive immunisation remains the protection of travellers to regions where hepatitis A is hyperendemic.[5,6] The incidence of infection with hepatitis A in unprotected travellers staying in international hotels in hyperendemic areas is estimated to be 3 - 6 cases/1 000 persons/month of stay. This increases to 20/1 000 for travellers eating and drinking in local establishments. With the exception of hepatitis B, which has a slightly higher mortality in expatriates, the morbidity and mortality of hepatitis A is greater than for any other preventable disease in travellers.[7]

Immune globulin (human immune serum globulin or gamma-globulin) (IG) given by intramuscular injection will protect against hepatitis for 4 - 6 months. Although experience indicates that 0,02 ml/kg of IG protects as adequately as larger doses,[8] more recent recommendations from the USA suggest a dose of 0,06 ml/kg.[5,6] This reflects the decreasing titres of antibody in the donor pool from which IG is prepared as the prevalence of hepatitis A decreases in the developed world. IG prepared in South Africa, where the disease prevalence is high, may be used in lower doses — 0,02 - 0,04 ml/kg for contacts and 0,05 - 0,06 ml/kg for travellers to endemic areas. The advent of a vaccine for hepatitis A should obviate the need for repeated doses of IG, since frequent travellers or those who intend spending more than 3 months in a hyperendemic area should be vaccinated against this disease.

Vaccination against hepatitis A

Several vaccines have been developed against HAV. Of these, Havrix (Smith Kline Beecham), a formaldehyde-inactivated vaccine prepared from HAV, has been released in South Africa. It is available as a 1 ml dose containing 720 ELISA units of hepatitis A viral protein. The immunisation schedule consists of two doses of 1 ml of vaccine, spaced 2 weeks to 1 month apart, given intramuscularly in the deltoid. A booster dose is given 6 - 12 months after the initial dose. This vaccination schedule is expected to provide immunity for up to 10 years. In haemodialysis patients and those with impaired immune systems adequate antibody titres may not be obtained after the primary immunisation course, and these patients may require additional booster doses. Havrix can be administered simultaneously with IG, although they should be injected at different sites. It is, however, not yet clear whether active immunisation is efficacious for post-exposure prophylaxis, and combining IG with the inactivated vaccine appears to depress the level of antibody response obtained.[9] An additional booster dose of vaccine may therefore be necessary. There appears to be no interference in the immune response to both antigens when hepatitis B vaccine is given concomitantly, although different injection sites are advised. Havrix is an inactivated viral vaccine and the risk to the fetus is considered negligible; however, it is not yet recommended in pregnancy. The effect in breast-fed infants has not yet been evaluated and it should therefore be

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used with caution in breast-feeding women. The vaccine appears to be well tolerated. Mild transient soreness and erythema at the injection site is the most common side-effect, while general complaints of malaise and headache are less common.[10]

Pre-exposure vaccination is advised for non-immune travellers to areas of high endemicity. This would include Africa, the Middle and Far East, central and south America and tropical islands. Workers in child care centres and in mental institutions and non-immune health care personnel should also consider vaccination. In order to prevent spread of infection, food handlers and kitchen workers should be considered for vaccination.

Mass vaccination of children, with appropriate boosters once the period of immunity is known, will not only decrease the morbidity and mortality due to HAV but will decrease the infectious pool and with it the risk of contracting the disease. Thus while routine immunisation of South Africans against HAV may not be as urgent as immunisation against the B virus, consideration should be given to including vaccination against hepatitis A in routine vaccination schedules.[11]

Post-exposure prophylaxis — passive immunisation

Post-exposure hepatitis A prophylaxis is provided via a single intramuscular dose of 0,02 ml/kg of the South African IG preparation. Immunisation is appropriate under the following circumstances:[5,6]

1. IG is recommended for *all* household and sexual contacts of persons with hepatitis A.
2. Day care centres, especially those attended by children in nappies, are important sources of HAV transmission. IG should be given to all staff and children as soon as an outbreak is recognised; in practical terms this means when hepatitis A is diagnosed in even a single child or employee, or if the disease is recognised in the households of two or more children attending the crèche.
3. Contact at primary and secondary schools and at colleges does not usually result in transmission of hepatitis A. Prophylaxis is not usually necessary unless a classroom-centred outbreak (hepatitis in 3 or more individuals) occurs, in which case IG should be considered for contacts.
4. Living conditions in institutions such as prisons and care facilities for the mentally disabled favour transmission of hepatitis A. When outbreaks occur IG should be given to inmates and staff. Depending on the epidemiological circumstances prophylaxis can be limited or can include the entire institution. With the introduction of hepatitis A vaccine, vaccination of non-immune staff should be considered.
5. Routine IG prophylaxis is not recommended for hospital personnel. Paediatricians and nurses in children's wards are invariably more exposed to hepatitis A and should be vaccinated if they are not immune.

The earlier IG is given in the post-exposure period, the more likely it is to have a protective effect. There is evidence that the course of hepatitis A can be prevented or attenuated by the administration of IG even after exposure to the virus, provided this takes place at least 2 weeks before the onset of jaundice.[12]

Hepatitis B virus (HBV)

The transmission of HBV by transfusion or accidental innoculation, during childbirth and through unprotected sexual intercourse is discussed elsewhere in this issue of the *SAMJ*. However, these do not explain the predominantly horizontal transmission of this virus seen in southern Africa.[13] Indeed, the prevalence of markers of current or previous infection in black South Africans is below 10% at 1 year of age but 70 - 80% in adulthood.[13,14,15] Whatever the mechanism, the data indicate that mass vaccination in the first year of life, by reducing the high incidence of hepatitis B,[16] might be expected to reduce the prevalence of chronic hepatitis B, cirrhosis and hepatocellular carcinoma.

The infectivity of patients with acute or chronic HBV infection correlates best with the amount of circulating virus, which may be determined by measuring HBV DNA.[17] However, for practical purposes persons with HBe antigen are usually more infectious than those with the corresponding antibody. Unfortunately traditional views on the importance of HBe antigen status in predicting both the progression of disease and infectivity have been challenged by the identification of HBe antigen-negative mutant viruses, which behave aggressively despite the lack of this serum marker in infected individuals.[18]

Pre-exposure prophylaxis — vaccination

Plasma-derived and recombinant HBV yeast-derived vaccines are considered equally safe and effective. Vaccine is given intramuscularly in the deltoid muscle and repeated at 1 and 6 months. Administration in the buttock is less effective and should be avoided. The dose is 20 g per injection in adults and 10 g in children.

Studies of the plasma-derived vaccine have shown that among susceptible healthy people who develop anti-HBs antibodies after the full 3-dose vaccine schedule, protective efficacy approaches 100%. This landmark study on HBV vaccine by Szmuness and co-workers also provided data suggesting that vaccination given after exposure may also be partially effective.[19,20] These data support the concept that anti-HBs antibody is the protective neutralising antibody and that vaccine-induced antibody confers protection against clinically apparent hepatitis B and the development of the HBs antigen-positive carrier state.

The protective efficacy of vaccination correlates with the strength of the immune response to the vaccine as measured by the titre of anti-HBs antibodies.[21] The critical antibody level above which near-complete protection against HBV infection is achieved is 10 mU/ml of anti-HBs. In a study of homosexual men at 5 and 7 years after vaccination when anti-HBs antibody had fallen below 10 mU/ml, protection against clinical HBV infection persisted.[22] Revaccination with a single booster dose results in a dramatic anamnestic response in those who have lost anti-HBs antibody.[23] At present there is no official guideline as to the timing of booster injections. For adults and children with normal immune status booster doses are not routinely recommended within 7 years after vaccination, and routine serological testing to assess antibody levels is not necessary during this period. Patients on haemodialysis appear to be protected only while they display titres over

10 mU/ml;[24] the suggested policy is to assess their antibody titres annually and to give booster doses when levels fall below this level.

Non-responders are defined as those who fail to develop protective titres of antibodies despite 4 injections. Various protocols, including a change from the recombinant vaccine to the plasma-derived vaccine, have been suggested to boost immunity in this group, but are of limited efficacy.

Who should be vaccinated?

In developed countries, where the incidence of hepatitis B is low and largely confined to certain well-defined risk groups, vaccination schedules were initially targeted at these groups. Thus the advisory committee on immunisation practices[5,6,25] has recommended that the following groups be vaccinated:

People at occupational risk. HBV infection is a major infectious occupational hazard for health care workers. The risk of acquiring HBV infection is dependent on the frequency of percutaneous and mucosal exposure to blood or blood products. The more likely the worker is to be exposed to blood or other fluids, the more urgent the necessity for vaccination. The risk of exposure is often higher in students than in qualified personnel, and vaccination should preferably be completed before students or trainees first come into contact with patients. Subgroups of staff at special risk include those working in mental institutions, where the virus may be spread by bites and assaults as well as by needle-stick injuries. People at lower risk who should also be vaccinated include those working in schools or sheltered workshops for the mentally disabled.

Patients at risk. Hepatitis B vaccination is recommended for susceptible haemodialysis patients. Although seroconversion rates and anti-HBs titres are lower than those for healthy persons, for those patients who do respond, hepatitis B vaccine will protect against HBV infection and reduce the necessity for frequent serological screening. Seronegative patients in mental institutions and special schools appear to be at lower risk than staff members but may also be vaccinated, as may patients in day-care programmes, particularly if they are in contact with aggressive patients who are carriers and may spread the virus by biting or scratching.

Recipients of blood products. Patients with clotting disorders who receive clotting factor concentrates have an increased risk of HBV infection and should be vaccinated.

Household and sexual contacts of HBV carriers. Household contacts of HBV carriers are at high risk of HBV infection. Sexual contacts, including spouses, boyfriends and girlfriends, appear to be at greatest risk. Condom use should be advised while vaccination becomes effective. When HBV carriers are identified, they should be educated about the condition and its spread, and all household and sexual contacts should be tested for anti-HBs antibody. Those who are negative are susceptible and must be vaccinated.

People in casual contact with carriers in schools and offices are at minimal risk of HBV infection, and vaccine is not routinely recommended. At child care centres, HBV transmission between children or between children and staff has rarely been documented. Unless special circumstances that might facilitate transmission exist, for example behavioural problems such as biting or scratching or medical conditions such as severe skin disease, vaccination of children in contact with a carrier is not indicated.

Those at risk of sexual transmission. Sexually active homosexual and bisexual men should be vaccinated as soon as possible, regardless of their age. Sexually active heterosexuals with multiple partners and prostitutes are also at increased risk, and vaccination is recommended for them; diagnosis of other sexually transmitted diseases should prompt consideration of vaccination. Those who are concurrently HIV-positive should be tested for anti-HBs antibody response after completion of the vaccine series, since their response may be suboptimal.

Drug abusers. Those using injectible drugs must be vaccinated as soon as possible.

Prisoners may be at risk because of drug abuse and homosexual activity.

International travellers. Vaccination should be considered for non-immune travellers who plan to stay for more than 6 months in endemic areas, and for short-term travellers who are likely to have intimate, and particularly sexual, contact with local people. Vaccination should begin at least 6 months before travel to allow for completion of the full series, but partial vaccination will offer some protection.

Other considerations. In the USA, it is recommended that children adopted from Africa or Asia should be screened for HBs antigen; if positive, the adopting family should be vaccinated. This is of limited applicability in South Africa which is in itself an endemic area.

In sub-Saharan Africa, where the prevalence of markers of previous hepatitis B infection exceeds 80%, a different approach is clearly necessary. Even in the USA, targeted vaccination has failed to reduce the incidence of hepatitis B.[26] The problem is exemplified by the observation that 90% of vaccine was administered to one group — health care workers — who account for less than 5% of the case load. Groups with higher prevalence, particularly drug abusers, prostitutes and homosexual men, are far more difficult to identify and vaccinate before transmission has occurred; in addition, many cases of hepatitis B do not fall into recognised risk groups.

Even in the developed nations one therefore cannot hope to control the disease by selective vaccination alone. Although vaccination must be offered to high-risk groups, universal childhood immunisation appears to offer the only chance of making an impact on the prevalence of hepatitis B, and the Global Advisory Group of the Expanded Programme on Immunisation (EPI) has now called for the incorporation of hepatitis B vaccination in all national immunisation programmes, with a target date of 1995 for endemic areas and 1997 for all others.[25,26]

Of course high-risk groups described above remain candidates for hepatitis B infection as much in South Africa as elsewhere, and should be considered for vaccination. Vaccination is clearly desirable for doctors, dentists, nurses, and students entering these professions. Patients on dialysis and haemophiliacs should be vaccinated. Family and sexual contacts of carriers must be tested and vaccinated, as should the homosexual community.

Age-specific data on the occurrence of hepatitis B and the prevalence of serological markers of HBV infection indicate that perinatal transmission of HBV is uncommon in South

Africa. Further, the incidence of HBV in the first 3 years of life is very low.[13,14] Hence a national hepatitis B vaccination programme providing universal coverage by the 3rd year of life would lead to the control of hepatitis B. Such a programme is currently being planned for South Africa and its implementation is imminent, probably in the second half of 1994.

Since there is much higher coverage for vaccines administered during the first 6 months of life than thereafter, when mothers may be less motivated to bring their children for immunisation, early administration of hepatitis B vaccine is preferable. However, increasing the number of vaccination visits in order to accommodate hepatitis B vaccination is to be avoided, since it will lead to lower coverage. Integrating hepatitis B vaccine into the vaccination schedule currently being used in South Africa is therefore optimally achieved by linking it with the polio/DPT schedule of vaccine doses at 3, 4½ and 6 months. This is the recommendation of the South African National Advisory Group on Immunisation. The seroconversion rate with this proposed schedule is only marginally lower than a 0-, 1- and 6-month schedule. The timing of booster doses, if necessary, is not clear at present and needs to be assessed in a cohort of vaccinees who received this schedule before a recommendation can be made.

Post-exposure prophylaxis

The risk of infection with hepatitis B may be reduced dramatically in people exposed to the virus provided that they are identified, tested and treated promptly. Most such people fall into one of two groups; health workers who suffer needle-stick injuries or accidental splashes or spills of blood or fluids from infected patients, and babies born to mothers carying the virus. Both passive immunisation with hepatitis B immune globulin (HBIG) and active immunisation with recombinant or plasma-derived vaccine are important in schedules of post-exposure prophylaxis.

HBIG is manufactured from plasma with high titres of anti-HBs antibody and contains an anti-HBs antibody titre more than 1 000 times that of conventional IG. Prompt immunoprophylaxis is necessary because the interval between exposure and antigenaemia can be as short as 6 days[27] and viraemia may develop even earlier. HBIG is therefore best injected within hours of exposure, but may be effective even when given within the first few days. Because its half-life *in vivo* is 17 - 25 days, a second dose of IG should be administered 30 days later. The recommended dose for adults is is 250 - 500 U; most preparations of HBIG contain 100 U/ml.

Accidental exposure

The protective efficacy of HBIG studied in a variety of post-exposure settings is of the order of 75%. There is good evidence that combined active-passive immunisation is considerably more effective than passive immunisation alone. In one study of staff in a renal dialysis unit following needle-stick injury, the risk of transmission of hepatitis B was 33% with passive immunisation alone, but only 4% with the combined schedule.[28] Contacts given HBIG should therefore be given hepatitis B vaccine at the same time, the HBIG and vaccine being given in different sites. The active vaccine must, however, be given in the deltoid and not the buttock for maximal efficacy.

The following protocol is recommended:[5,6]

For exposed people who have not previously been vaccinated, test the serum of the exposed person for anti-HBs antibody and the serum of the source for HBs antigen. If the exposed person has seroprotective titres of anti-HBs antibody, no further therapy is necessary. If a rapid result cannot be obtained, administer a single intramuscular dose of HBIG (0,06 ml/kg) within 24 hours of exposure, or as soon as possible.

Where the source is proved to be HBs antigen-negative, the source is non-infectious and no immediate further action is necessary. However, if the exposed person is anti-HBs antibody-negative, it is wise to commence conventional vaccination as soon as possible to protect against future exposure.

Where the source is proved to be HBs antigen-positive, and the exposed person does not have protective titres of anti-HBs antibody, HBIG, if not already administered, is given and active immunisation using an accelerated, 4-dose schedule is started. The first dose of HBV vaccine is given intramuscularly at a different site to the HBIG within 7 days of exposure, and 3 further doses are given at 1, 2 and 6 months. When combined with the vaccine, a second dose of HBIG at 4 weeks is not required for otherwise healthy individuals.[29]

Where the HBs antigen status of the source cannot be determined, it is wise to assume that it was positive. If the exposed person is susceptible, administer both HBIG and the accelerated schedule of HBV vaccine. If it is thought to be very unlikely that the source was an HBsAg carrier, use of HBIG may be omitted, but the vaccine should still be given.

For exposed people who have previously been vaccinated, test the serum of the source for HBs antigen and the serum of the exposed person for anti-HBs antibody.

Where the source is HBs antigen-positive, and the exposed person received either full or partial immunisation, it is necessary to find out whether protective levels of anti-HBs antibody are still present by determining the titre. If anti-HBs is adequate, no treatment is indicated. If anti-HBs titres are below the protective threshold, give HBIG and a single dose of vaccine at separate sites. Where anti-HBs antibodies are undetectable, give HBIG as soon as possible and commence the full accelerated schedule of vaccination.

If levels of anti-HBs antibodies have been tested and found to be seroprotective within 12 months before exposure, it is unnecessary to retest them; the patient is immune and no further action is necessary. Similarly, if it is known that adequate anti-HBs levels were demonstrated after vaccination, even if more than 12 months previously, a single booster dose of vaccine will ensure that levels are adequate and may be given instead of determining the titres at this stage. If the exposed person had previously been vaccinated with 4 or more doses of vaccine but did not demonstrate protective titres, he or she is a non-responder who is at risk of infection. Two doses of HBIG (the first as early as possible, the second a month later) should be given.

If the exposed person had received fewer than 3 doses but shows adequate levels of anti-HBs antibody, it is sufficient to complete the course of vaccination. If levels are inadequate give HBIG (0,06 ml/kg) as soon as possible and then complete the vaccine schedule.

Where the source is HBs antigen-negative, no further action is necessary. People who have not received a full course of vaccine should complete the course.

Where the source cannot be tested, it is wise to consider it as positive and continue as outlined above, which will in any event ensure that the exposed person will be adequately protected in the event of a further accident. Known vaccine non-responders should receive HBIG as early as possible; a second HBIG dose, 1 month later, is optional.

Perinatal exposure

Vertical transmission of HBV from mother to infant during the perinatal period usually has severe sequelae. Infants born to HBe antigen-positive mothers have a 70 - 90% chance of acquiring perinatal HBV infection. It is known that 85 - 90% of infected infants will become chronic HBV carriers[30] and it is estimated that 25% of these carriers will die from cirrhosis or primary hepatocellular carcinoma. Infants born to HBsAg-positive, but HBe antigen-negative mothers have a lower risk of acquiring perinatal infection. Although prenatal screening of all pregnant woman would identify those who are at risk, the low incidence of perinatal transmission in South Africa coupled with the low HBe antigen prevalence in pregnant women[31] make antenatal screening for hepatitis B an unwarranted and cost-ineffective strategy in this country at present.

Treatment of the infant born to the HBe antigen-positive mother with HBIG and hepatitis B vaccine is 85 - 95% effective in preventing the development of the HBV chronic carrier state. For the prevention of perinatal transmission from HBe antigen-positive mothers, HBIG in a dose of 200 U should be given together with active immunisation within 12 hours of birth[29] and preferably within the first hour. HBV vaccine is given at the same time at a separate site and repeated at 1 and 6 months after the first dose. Breast-feeding is not contraindicated.

Safety of human serum IG and hepatitis B hyperimmune globulin

The frequency of adverse reactions is about 1% in recipients of intramuscular IG. These are generally limited to pain and tenderness at the injection site. Haematomas are seen occasionally, especially in patients who are receiving anticoagulants. The few reported cases of anaphylactic shock may have been due to inadvertent intravenous injection. It should also be noted that intravenous preparations of gamma-globulin are inappropriate for the prophylaxis of hepatitis. Angioneurotic oedema may also develop in a few patients. Both the plasma-derived and recombinant hepatitis B vaccine appear to be extremely safe. Of 41 possible adverse neurological events reported after 850 000 vaccinations with the plasma-derived vaccine, it was considered that none were causally related to the vaccine.[32]

Both immune globulin and HBIG, and indeed the plasma-derived hepatitis B vaccine, are prepared by methods which will inactivate retroviruses.[33] Transmission of the human immunodeficiency virus (HIV) has never been reported[34] despite widespread use of these preparations, and they should never be withheld because of fear of HIV infection.

Hepatitis C (HCV)

Currently patients receiving blood products constitute the only group at risk of hepatitis C infection, which is readily recognisable and hence potentially amenable to pre-exposure prophylaxis. Some early work suggested that administration of immune serum globulin before transfusion might reduce the incidence of post-transfusional non-A, non-B hepatitis.[35,36] However, the need for this crude form of pre-exposure prophylaxis has fallen away with the introduction of routine screening of blood donors for HCV. There are likewise no data to support the use of IG for post-exposure prophylaxis, and it is not recommended.[37]

Hepatitis D (HDV)

Passive immunisation for the prevention of HDV infection is not available, and anti-HDV has not been shown to be a neutralising antibody. However, the disease is eminently preventable, since HDV cannot survive except in the presence of co-infecting HBV. Measures to prevent initial infection with HBV will therefore be equally effective against hepatitis D. Hepatitis D is not a problem in South Africa. In countries where it is encountered, it is largely a disease of intravenous drug abusers. Vaccination of this group against hepatitis B will substantially diminish the pool of HDV in the community; universal vaccination against hepatitis B may eventually eradicate it.

Hepatitis E (HEV)

There is no evidence to suggest that immune globulin will prevent hepatitis E infection. Although immune globulin prepared in developing countries where the disease is endemic is likely to have specific antibodies, a report from India indicates that immune serum globulin is useless in preventing transmission of the disease.[38] In any case no vaccine is available, and the only measures recommended for the prevention of HEV infection are those relating to good personal hygiene and the prevention of contamination of food and water supplies.

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