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HEPATITIS B

This document is presented in response to a request of the 95th Meeting of the Executive Committee of the Pan American Health Organization, held at the Headquarters building in Washington, D.C., from 24 to 28 June 1985, that an item on the control of hepatitis be included in the Provisional Agenda of the XXXI Meeting of the Directing Council

Viral hepatitis is a serious public health problem and a major contributor to morbidity and mortality in many areas. Incidence rates of acute viral hepatitis are highest in temperate South America, reaching two to three times those in the United States of America and Canada. Rates reported in Central America are also above those reported in the United States, and those in the Caribbean tend to vary, with the lower rates in the smaller countries. The majority of the cases reported are in children under 15 years of age and, of those, 78-85% are due to hepatitis A virus (HAV). Hepatitis B (HBV) and non-A, non-B (NANB) are less frequent causes of acute illness. In adults, there is no clearly observed predominance of any of the three types.

Control of HBV has relied on prevention of transmission and the development of a vaccine which is produced in the Region only by the United States of America.

Control of HAV is effected mainly by sanitation and the administration of normal immunoglobulins which provide a relatively short-lived protection, but with the technology available, the development and use of a vaccine is feasible, and currently several are being tried.

Over the past 30 years, WHO has convened several meetings of experts to review advances in diagnosis and control, promoted training in laboratory techniques, supported field research and established a network of collaborating and national reference centers. More recently, however, WHO has launched a viral hepatitis program, which focuses on regional production and distribution of low cost HBV vaccines and diagnostic reagents, operational research on the epidemiology of HBV and appropriate strategies for vaccine utilization, development of national HBV control programs, and basic research on viral hepatitis.

PAHO collaborates with the countries of the Region in the promotion of these activities, has established centers of expertise in the study of hepatitis and is cooperating in the production and distribution of reagents. The major emphases for the future should be on laboratory based activities, epidemiological activities including implementation of general public health measures for control of the hepatitides, and HBV vaccination strategies, including vaccine production and the development of national control programs for its application.

The Directing Council is being asked to examine the problem posed by viral hepatitis and consider appropriate approaches to be taken.

PROSPECTS FOR THE CONTROL OF HEPATITIS IN THE AMERICAS

Introduction

Viral hepatitis is currently a major cause of acute and chronic illness and mortality in all parts of the world. Several causative agents--hepatitis A virus (HAV), hepatitis B virus (HBV), and delta virus--are well characterized, and at least three others, currently defined as non-A, non-B agents (two blood transfusion-associated and one epidemic form) are being studied. While hepatitis A is known to cause only acute hepatitis, primarily in children worldwide, both hepatitis B and the post-transfusion-associated non-A, non-B agents have been associated with a chronic carrier state and with long-term consequences such as chronic hepatitis and cirrhosis. In addition, HBV infection is strongly associated with primary hepatocellular cancer (PHC), and is the major cause of this cancer worldwide. Most PHC cases have HBV detectable in serum and HBV-DNA integrated in liver tissue; prospective studies in Taiwan and Japan have estimated that the relative risk of HBV carriers developing PHC is over 200 times that of other persons.

The recent development of safe and effective vaccines for hepatitis B now provides the critical tool for control of this health problem worldwide and has the potential to eradicate hepatitis B as a disease in man. The World Health Organization has developed a global program for control of hepatitis B, and has urged development of regional programs with several major foci, including regional production and distribution of low cost HBV vaccines and diagnostic reagents, operational research on the epidemiology of HBV, and appropriate strategies for vaccine utilization, development of national HBV control programs and basic research on viral hepatitis.

Some countries with high HBV disease endemicity are now undertaking substantial programs to control this disease. In these countries, efforts are focusing on prevention of perinatal and early childhood infection, which are associated with a high risk of development of the HBV carrier state and subsequent death from chronic liver disease and cancer. In such areas, the estimated lifetime risk of death due to cirrhosis or primary hepatocellular carcinoma may be 25% for those infected early in life.

Epidemiology of Hepatitis in the Americas

Viral hepatitis is a serious public health problem in the Americas, and is a major contributor to morbidity and mortality in many areas. The true impact of the disease, however, has not been determined

in many countries of the Region. Among the factors that contribute to this lack of knowledge are: 1) deficient epidemiologic information due to inadequate surveillance in some countries; 2) difficulties in establishing correct clinical diagnoses due to inadequate laboratory diagnostic support; and 3) failure to assess adequately the incidence and causes of chronic hepatitis, cirrhosis and primary liver cancer. Sero-epidemiologic data for both HAV and HBV are limited and do not yet accurately define the real extent of these problems. Nevertheless, information is available to permit general observations about the epidemiology of hepatitis A and B and to allow some conclusions about that of delta and non-A, non-B hepatitis (NANB).

Incidence of Acute Hepatitis

Acute viral hepatitis is a disease reportable to the national health authorities throughout most of the Americas. National statistics are available from almost all countries in South America, Central America, the Caribbean region, and North America. In the past, few countries outside the United States of America and Canada have differentiated cases according to type (A, B, NANB), since serologic tests are not widely available to allow accurate determination of hepatitis types. Furthermore, it must be assumed that underreporting of diseases is high in all areas.

Generally, incidence rates of acute viral hepatitis are very high in South America, ranging from rates of 24 in Venezuela to 93/100,000/year in Uruguay (Table 1). Rates are highest in temperate South America, reaching 2-4 times those in the United States and Canada; in all such areas the majority (50-85%) of cases are reported in children under age 15. Areas reporting lower diseases rates include less populous countries such as Bolivia, Paraguay, Ecuador and Guyana; in these areas it is likely that disease reporting is less successful. Rates reported from Central America also tend to be above those in the United States, with the exception of a low rate in Guatemala; as in South America, the majority of cases occur in children under age 15. Finally, rates reported in the Caribbean are variable, ranging from very high levels in Cuba and the Dominican Republic to low levels in most smaller Caribbean countries.

Serologic testing of cases of acute hepatitis for markers of both HAV and HBV has been reported from large cities in certain countries--Chile, Argentina, Brazil, Costa Rica, Colombia, and several sites in the United States of America (Table II). Data are reasonably consistent. In children under age 15, the majority of hepatitis is due to HAV (78-85%). Both hepatitis B (1-16%) and non-A, non-B (5-20%) are less frequent causes of acute illness. In adults, frequencies of hepatitis types are more variable, and more balanced among the 3 types, with HAV accounting for 27-71% , HBV 7-67% and NANB 5-25% of acute hepatitis cases.

Hepatitis A

Serologic prevalence studies indicate that HAV is an infection of childhood in the whole Region, with the exception of the United States of America, Canada and possibly the smaller Caribbean islands. In one study, the prevalence of anti-HAV in adult blood donors was above 95% in almost all countries. Although data for children are not available for most areas, studies of children from Mexico and Chile show that the infection is acquired at an earlier age in lower socioeconomic classes, with lower classes reaching 95% infected during preschool years but with middle or upper classes not reaching this level until later school years.

Incidence rates of HAV are not available directly; nevertheless, given that most hepatitis in the Region occurs in children under age 15, and that the majority of such hepatitis is due to HAV, we can predict that the majority of cases of symptomatic acute viral hepatitis are due to HAV. Indeed, using numbers of reported cases and serologic data from studies of acute hepatitis in Chile, we estimate that 80% of hepatitis in that country is due to HAV, and that the rate of HAV disease presently reported is 40/100,000/year, three times that of the United States of America. It is likely that this reasoning would apply to most other countries, and that the incidence of acute hepatitis A disease in the Region is much higher than in the United States and Canada.

Outbreaks of hepatitis A have been reported from several countries (Argentina, Brazil, Costa Rica, Panama) of the Region, some of which are possibly due to waterborne transmission.

Hepatitis B

The prevalence of HBV surface antigen (HBsAg) in blood donors using sensitive assays (RPHA, RIA or ELISA) ranges from low (0.3%) to very high (> 10%) within the Region. In most areas, levels are low-moderate (0.5-3.0%), but in certain areas rates are much higher (Table 3).

In South America, HBsAg prevalence increases from south to north, from 0.5-1.1% in temperate regions (Chile, Argentina, Uruguay and southern Brazil) to moderate levels (1.5-3.0%) in central and north-eastern Brazil, and in the cities of the Andean countries except Chile. Very high prevalences (5-15%) of HBsAg have been observed throughout the Amazon region of Brazil, and in some regions of Colombia, Peru and Venezuela. In Central America, HBV prevalences are low (Mexico) or moderate (1.0-3.0%), as they are in the Caribbean (1.0-2.0%), with the exception of Hispaniola, where both Haiti and Dominican Republic have high disease prevalence. Recently a high prevalence of HBV was documented in St. Christopher/Nevis. Prevalence of HBsAg in the United States and Canada is very low (0.3%), except in specific high risk groups.

The available data are often limited to studies of blood donors from one or two large cities in each country. Almost no data on HBV prevalence by age, race, urban vs. rural status or socioeconomic level is available for any country outside the United States of America and Canada. In South America only Argentina and Brazil have reported data by sensitive tests from more than a few localities. Data from Brazil suggest higher prevalence in low socioeconomic classes and in persons of black or mixed as opposed to Caucasian origin. Studies of indigenous peoples from Brazil, Colombia, Panama and Venezuela generally show very high HBsAg prevalences. Geographically, the widest variation in prevalence has been observed in Brazil. However, regions of Colombia (Santa Marta region), Venezuela (indigenous Indians) and Peru (Amazon Basin) have very high disease prevalences, and the northern-most parts of Chile and Argentina may have higher prevalences than the central and southern regions of these countries.

Persons who belong to high HBV risk groups in the United States of America and Canada also appear to be at increased disease risk in South America. Studies of health care workers (Brazil, Chile, Argentina) suggest 1.5-2-fold higher risk than local populations. Hemodialysis patients (Brazil, Argentina, Colombia), homosexuals (Brazil, Chile) and mentally retarded children (Brazil) all appear to be at very high disease risk. In addition, prostitutes and diabetics may be at excess risk above the general population.

Few studies of HBV transmission have been completed in the Region. Presumably transmission occurs by the same routes described in other parts of the world--by percutaneous or permucosal exposure to infective blood or other body secretions. In adults, the predominant routes of transmission might be sexual contact (heterosexual or homosexual) and contact with contaminated needles (either for illicit drugs or due to inadequate sterilization). In high endemicity areas in which disease transmission occurs among children, transmission might be perinatal, via contamination of open skin wounds, or possibly via contaminated needles or even insects. The importance of these routes, particularly the role of perinatal transmission, needs to be assessed in such areas. Outbreaks of hepatitis B due to contaminated immune globulin have been reported from Brazil.

The consequences of hepatitis B infection in causing acute hepatitis, chronic active hepatitis (CAH) and cirrhosis, and primary hepatocellular carcinoma (PHC), have been assessed by measuring the proportion of cases of each disease that are due to hepatitis B. Studies from large cities in several countries have shown HBV infection to account for only 1-16% of acute viral hepatitis in children; nevertheless, in adults HBV infection accounts for a significant proportion (25-67%) of disease in all areas studied except in Chile (7%) (Table 2). Other studies have shown HBV infection in 15-63% of

cases of CAH and cirrhosis, and in 12-70% of PHC cases. Reporting of cirrhosis as a cause of death in the Region shows rates that vary widely, from levels similar to those in the United States of America to 3-4 times higher (Chile, Colombia). In a hospital in Manaus, a large city in the Amazon region of Brazil, liver cirrhosis is the main cause of death. Population-based studies of PHC incidence are available from only seven areas, all with low-moderate HBV endemicity, and show rates which are similar to those of the United States of America and Europe, and much lower than those in South-east Asia and Sub-Saharan Africa. However, no population-based data on cirrhosis and PHC from high HBV prevalence areas are currently available.

Delta Infection and Fulminant Hepatitis

An unusual type of fulminant hepatitis (severe hepatitis resulting in encephalopathy or other signs of hepatic insufficiency) has been documented to occur in three localities in this Region. In two areas--the Santa Marta region of Colombia and the Amazon Basin--severe hepatitis has been described for over 40 years and distinct entities are known as Santa Marta hepatitis and Labrea hepatitis, respectively. In addition, a severe hepatitis epidemic occurred during 1979-1981 among the Yucpa Indians in western Venezuela. Recent studies have documented that all occur in areas of high HBV endemicity, where 5-15% of the population are HBsAg carriers and in which HBV infection occurs during childhood. Studies in Venezuela have shown that outbreak to be due to delta infection of hepatitis B carriers. Other studies have shown delta virus infection to be highly endemic in the Santa Marta region and in the Amazon Basin, and it is currently suspected that delta is in part (or fully) the cause of Santa Marta and Labrea hepatitis.

Studies of HBV carriers in Chile and the United States of America showed 5% to be positive for delta, while in Rio de Janeiro no delta positive persons were found among 200 HBV carriers. In Argentina, about 15% of cases of HBsAg positive CAH show delta positivity. In contrast, studies in high HBV endemicity regions show higher prevalence of delta infection. Studies in the Amazon Basin have identified the presence of delta in at least 15 localities, including Manaus. In general, positivity is found in 20-30% of HBV carriers and acute hepatitis cases, 85-90% of cases of CAH and cirrhosis, and 30-50% cases of fulminant hepatitis B in this Region. Studies in Venezuela indicate that delta virus continues to spread among Yucpa Indians who are HBV carriers, and that 5-10% of susceptible HBV carriers become infected yearly. Delta virus infection is also present in the Santa Marta region of Colombia, and is found with highest frequency in villages with fulminant Santa Marta hepatitis.

Non-A, Non-B Hepatitis

Non-A, Non-B hepatitis has been identified in several studies of acute hepatitis cases, and appears to account for 5-20% of hepatitis in

children and 20-30% of hepatitis in adults in most local studies (Table 1). In most studies, NANB is associated with prior transfusion or needle exposures; however, evidence from Costa Rica and Argentina suggest that person-to-person or waterborne transmission may occur. We may presently conclude that blood-borne non-A, non-B agents are certainly present and account for significant hepatitis morbidity among adults in the Region; infection with the fecal-oral non-A, non-B agent may occur, but there is no clear documentation of this at present.

PROSPECTS FOR THE CONTROL OF VIRAL HEPATITIS

Hepatitis B

Control of hepatitis B has, in the past, relied on several measures, including screening of donated blood for HBsAg to prevent post-transfusion hepatitis, sterilization of reusable needles and instruments and/or use of disposable needles, environmental control in settings such as hemodialysis units, and use of specific immunoglobulins (HBIG) for post-exposure prophylaxis. Such measures continue to be effective and important for prevention of hepatitis B.

The development of hepatitis B vaccine provides the most effective tool in the prevention of hepatitis B. Active immunization with hepatitis B vaccine not only has the capability to reduce the frequency of overt disease, but is the only method which offers the capability of eradicating this disease.

Several hepatitis B vaccines prepared from plasma of chronic carriers of HBsAg have been shown to be safe, immunogenic and highly effective. When given prior to exposure, they are more than 95% effective in preventing infection. When given immediately after exposure, they are at least 75% effective in preventing infection or development of the chronic carrier state. The imminent licensure of additional plasma-derived vaccines, as well as vaccines prepared by DNA recombinant technologies, suggests that within the next few years this vaccine will be readily available and cheap.

1. Active Immunization

The initial choice facing national authorities is whether to import vaccine, commence production locally, enter into an agreement with a foreign manufacturer in which starting plasma is provided in return for finished product, or to produce vaccine locally under license. Although decisions of this magnitude require an evaluation of national economic and technical structures and priorities, certain principles are clear. To produce hepatitis B vaccine locally, countries must have the capability of making complex biological products, and a national control authority capable of measuring vaccine potency and monitoring production standards.

In the Americas, the only hepatitis B vaccine currently being produced comes from the United States of America. In South America, economic factors have prevented national health authorities from embarking on control programs, and it is unlikely that a significant increase in usage will be achieved until the vaccine is produced in the Region either on a national or regional basis. Several countries in South America are capable of producing hepatitis B vaccine. Argentina has already produced one experimental batch, and Brazil has studied HBsAg purification methods essential for vaccine production.

While currently licensed hepatitis B vaccines are manufactured from human plasma, vaccines produced by DNA recombinant technology will be available in the next few years. A number of countries have delayed the introduction of hepatitis B control programs until these newer vaccines become available, on the grounds that they wish to utilize the most modern technology available. Such delays should be discouraged and control programs utilizing plasma-derived vaccines should proceed as rapidly as possible.

Countries, whether importing vaccine from abroad or producing it locally, should have appropriate procedures for determining that vaccine meets appropriate standards of safety and efficacy.

2. Immunization Strategies

A variety of strategies have been suggested depending upon the prevalence of hepatitis B infection. Canada, the United States of America, Argentina, and Chile are countries in which the prevalence of infection is generally low, while a number of countries in Central and South America fall into the intermediate category. In some regions of South America, particularly the Amazon Basin, the prevalence of hepatitis B infection is as high as that in South-east Asia or tropical Africa. Vaccination strategies adopted by national health authorities are likely to vary from limited administration to specific high-risk groups to widespread immunization in infancy and early childhood. In countries or regions where hepatitis B is hyperendemic, the most effective way of controlling infection and reducing the incidence of long-term sequelae is by immunization of all newborn babies shortly after birth.

Data which national health authorities require prior to development of a control program include:

- Age-specific prevalence of HBsAg and anti-HBs in various segments of the population;

- Prevalence of HBsAg and HBeAg in women of childbearing age.

- Number of births per year and the proportion which occur in medical facilities.

- Status of current infant immunization programs, especially the efficiency of coverage under the Expanded Program on Immunization (EPI).

Additional components are considered desirable to underpin a national hepatitis B control program, including:

- A surveillance system capable of monitoring the incidence of acute hepatitis B and, if possible, chronic active hepatitis, cirrhosis, and liver cancer in the population.

- A control authority capable of assuring appropriate quality control of hepatitis B vaccines.

- A reference laboratory capable of evaluating immune response and persistence of immunity in populations undergoing vaccination.

- An adequate vaccine delivery system capable of efficient immunization of infants, preferably as part of the EPI program.

Hepatitis A

The efficacy of normal immunoglobulins (IG) for preventing hepatitis A is well established. Such globulins administered before exposure or within one or two weeks following exposure can prevent or modify the severity of infection with HAV. However, protection is relatively short-lived and most exposures to HAV are unrecognized. Therefore, IG has limited value in national programs for the control of HAV.

Although a licensed hepatitis A vaccine is not yet available, development and use of such vaccines are now considered feasible, and several vaccines are under development.

Live, attenuated hepatitis A vaccines would be especially useful in developing regions of the world. Live vaccines would be relatively inexpensive and would probable require only one orally administered dose that would provide not only systemic protection but also enteric immunity. However, an enteric site of HAV replication has never been identified and the importance of enteric immunity is therefore speculative.

The development of killed whole-virus vaccines is also being pursued. The advantage of such vaccines would be a greater margin of safety, since the inactivation step would prevent reversion to virulence

of the HAV strain as well as infection with potential contaminants. Disadvantages would include high cost because of relatively poor growth of the virus in tissue culture and the requirement for multiple doses of the vaccine to stimulate adequate immunity. In addition, such a vaccine would have to be administered percutaneously. Killed hepatitis A vaccines are being developed and are in preclinical stages of evaluation.

Recombinant DNA technology has provided additional avenues to vaccine development. However, such approaches are in early stages of development.

Diagnostic Reagents

The continuous availability of high quality reagents is essential to collect reliable data on the prevalence of hepatitis infection, to study the epidemiology and mode of spread of the diseases and to develop and monitor control programs. The existence of specific and sensitive laboratory tests makes it possible to determine the contribution that infection with HAV, HBV, NANB and delta virus make to acute and chronic liver diseases. A variety of assays for detecting these infections is now available in the Region, primarily imported from commercial manufacturers located in Europe, Asia and North America. The costs of these tests are beyond the reach of most countries in the Region.

PAHO has already established centers of expertise in the study of hepatitis and is cooperating in the production and distribution of reagents throughout the countries of the Region. Individuals countries should consider several options for provision of diagnostic testing, such as a) purchase of kits and reagents from outside the country; b) full production by official institutions; c) establishment of partnerships between the private and public sectors; d) private enterprise within the country with official inducements; e) establishment of intercountry programs.

Two issues which must be addressed concurrently with development of reagents are the different priorities for development of specific tests and the standards of sensitivity and specificity for these tests. The most urgent need is for wide availability of a sensitive test for HBsAg, for use in screening of blood prior to transfusion, and screening of women for prevention of perinatal HB transmission. Of the third generation tests for HBsAg detection, reverse passive hemagglutination (RPHA) can detect about 5 ug/ml of HBsAg, whereas enzyme immunoassay (EIA) will detect less than 1 ug/ml. It is estimated that most blood positive for HBV will contain HBsAg at concentrations greater than 10 ug/ml, and therefore detectable by RPHA.

Additional tests of importance for epidemiologic studies, immunization assessments, and diagnosis of acute hepatitis include those for anti-HBs, anti-HBc, IgM anti-HAV, and antibodies to delta virus.

Development of diagnostic tests of high sensitivity, ideally equivalent to the currently available EIA assays in North America, should be the second priority for laboratories of the Region.

The choice of particular test systems will be guided by factors such as availability of good quality plastics, difficulties in disposing of radioisotopes and preferences of local laboratory workers. The tests chosen should be sensitive, specific, simple and cheap, and capable of being performed by laboratory workers with limited training and facilities.

If a country elects to produce its own reagents, their quality should be checked by collaborative studies organized through the PAHO network. Local quality control programs should also be established to ensure that the tests continue to be of high standard and are performed accurately throughout the country.

STRATEGIES FOR THE PREVENTION AND CONTROL OF HEPATITIS IN THE AMERICAS

For almost 30 years WHO has been actively involved in the field of viral hepatitis. Specially convened groups of experts have regularly reviewed advances in the field with particular emphasis on diagnosis and control, and have prepared pertinent publications. In addition, WHO has promoted training in laboratory techniques for the diagnosis of diseases, supported field research, and established a network of collaborating and national reference centers.

In view of the magnitude of the problem and the present and upcoming technological advances toward the control of viral hepatitis, WHO is launching a viral hepatitis program. In July 1983 an Advisory Group on the development of such a program met in Geneva and proposed the following overall objectives:

1) Define the natural history of viral hepatitis in all regions of the world, and in particular determine ways in which the agents are spread and the mechanisms by which they produce disease.

2) Assist in the development and evaluation of safe, effective, and inexpensive means of preventing the disease and treating its long-term sequelae, including hepatocellular carcinoma.

3) Promote and assist in the application of these methods in countries in which viral hepatitis is a public health problem.

In addition, the Group defined targets and activities. Two main targets were envisaged: strengthen diagnostic capabilities, such as epidemiological surveillance, define population groups at special risk of infection, etc.; and reinforce general sanitation and environmental

procedures, immunization, treatment, and other control efforts. Six main activities were identified: surveillance and epidemiological studies; information exchange, and dissemination; training; reagents production; development of field trials for immunization; and standardization of immunoglobulins and vaccines.

Over the years, PAHO has assisted countries of the Region in promoting some of these activities, but perhaps the time is now appropriate to promote more vigorously in a programmed way the activities necessary for the prevention and control of hepatitis.

The major emphases for work on viral hepatitis in the Region should center on three types of activity: a) laboratory based activities, b) epidemiological activities including implementation of general public health measures for control of the hepatitides; and c) hepatitis B vaccination, including both vaccine production and development of national control programs to utilize vaccine. Prioritization of these activities must take into consideration that both hepatitis A and hepatitis B are major public health problems in most of the Region, that a safe and effective hepatitis B vaccine is already available and that technology to produce cheaper vaccine is becoming available, and that a hepatitis A vaccine is likely to be available in the near future. Given the present availability of a hepatitis B vaccine and the demonstrable acute and chronic consequences of HBV infection, major emphasis must be placed on hepatitis B activities in all areas. However, activities focused on other types of hepatitis, particularly hepatitis A, should not be neglected.

a) Laboratory Activities

A program for development of laboratory capabilities in the Region has been under way for several years, and has consisted of regional training courses in inexpensive EIA methodologies and direct consultation with individual groups on reagent and test development. Such programs are critical because the high cost of commercial tests produced in the US and western Europe preclude their wide use in the Region, and the need for tests of high sensitivity to accurately assess the epidemiology of these diseases. To date, as recommended by WHO Expert Committees on Rapid Viral Diagnosis, the program has focused on development of generic EIA assays for HBsAg; this test is the most critical for use in blood banking, vaccination programs and epidemiologic studies of HBV. Specific difficulties with this program have been summarized recently, and include the nonavailability of ultracentrifuges to prepare reagents in some areas, insufficient laboratory expertise in some areas, and the nonavailability of high quality, low cost plastics for testing. Proposed solutions are to focus reagent production in several high quality regional facilities, and to work with manufacturers to develop appropriate locally produced plastic products.

Other considerations in laboratory programs include developing appropriate strategies of laboratory support for smaller countries of the Region with particular emphasis on Latin America, and on evaluating the potential roles of government-sponsored laboratories and private companies in the large-scale production of reagents. Smaller countries cannot be expected to have the equipment (ultracentrifuges) necessary to produce high-quality reagents, and so production of reagents and tests may need to be done in larger countries having appropriate facilities. While government supported laboratories in larger countries may be expected to play a lead role in test development, in small-scale reagent production and in quality control, the need for private company involvement in large-scale reagent production needs to be considered. Additional activities in laboratory programs could include assessment of present facilities of research laboratories and blood banks for HBsAg testing, evaluating methodologies used, quality control, resources and future capabilities.

Development of other tests for epidemiologic and diagnostic uses is also important. Sensitive tests (EIA or RIA) for either anti-Hbs or anti-HBc are necessary for epidemiologic studies of hepatitis and vaccination screening programs; such tests would facilitate epidemiologic studies by reducing sample sizes necessary to demonstrate and differentiate levels of disease endemicity. Tests for markers of delta infection are critical to define the importance of this agent as a cause of fulminant and chronic hepatitis in the Region, especially in high HBV endemic areas of South America. A test for IgM anti-HAV is necessary to better define the importance of both hepatitis A and non-A, non-B as causes of acute hepatitis in the Region. Development of these tests should be given high priority. Development of other tests, such as IgG anti-HAV, HBeAg and anti-HBe, and IgM anti-HBc may be important for epidemiologic studies in the future, but are presently of low priority.

b) Epidemiology

The second focus for activities in the Region should be on epidemiologic and public health activities. As stated previously, accurate epidemiologic studies are a necessary basis for devising disease control programs; present data are largely limited to information on blood donors in large cities, and may not be applicable to the whole population of a given country.

Priorities should include country-wide studies of HBV prevalence which provide data by age, race, geographic region, urban vs. rural, and socioeconomic status, and additional studies of "high" risk groups (homosexuals, health care workers, etc.). In addition, detailed studies in high HBV endemicity areas are needed to determine the typical age of infection, importance of mother-to-infant transmission, and chronic disease morbidity and mortality. The latter should be coupled with

studies of delta infection to more clearly define the importance of this disease. Studies of delta prevalence need to be conducted in samples of HBV carriers, chronic HBV cases, and acute and fulminant hepatitis B cases in areas of low and high endemicity. Finally, serologic studies of acute hepatitis cases are needed to define the nature and importance of non-A, non-B hepatitis in the Region.

Another epidemiologic focus should be on national programs for hepatitis surveillance, prevention and control. Development or improvement of reporting systems will be important in assessing the impact of acute hepatitis in the Region, especially in providing a basis for hepatitis A control programs when a vaccine becomes available. Assessment and strengthening of current programs for control of hepatitis A (sanitation, etc.) and hepatitis B (including HBsAg screening of blood and blood products, and sterilization or use of disposable material in hospitals, clinics and laboratories) should be implemented.

c) Vaccine Production

The third focus should be on the development of vaccination programs for reduction of hepatitis B. An efficacious vaccine is now available, and national vaccination programs can be expected to significantly reduce the burden of disease. The major reservoir of infection is HBV carriers; and since there is at present no means to terminate the HBV carrier state, the reservoir for infection and the pressure for HBV infection can be expected to remain constant during the initial years of HBV vaccination programs. Because of this, it will take one or more generations of intensive vaccine use to have major impact on the disease. However, target programs in specific high risk groups can be expected to have more immediate impact. For this reason efforts to begin control of the disease are necessary in all areas, and especially in areas of moderate or high risk of infection. Strategically, rapid initiation of control efforts is desirable to begin to reduce the overall burden of HBV carriers and of chronic HBV disease.

One critical consideration is the need for and availability of less expensive vaccines. Regionalization of production of plasma-derived vaccines as well as imminent availability of DNA recombinant vaccines to be produced by several manufacturers may be expected to dramatically reduce the per dose cost of vaccine within the next several years. This cost reduction is currently evident for plasma derived vaccines in some areas of the world. For example, one manufacturer in Europe is now supplying bulk vaccine to Taiwan at a cost of US$4.00 per dose, and a vaccine licensed in South Korea is being sold in that country for less than US$12.00 per dose. One U.S. manufacturer has supplied vaccine to the Hong Kong government for less than half of the U.S. market price for the same vaccine. The potential and need for additional production of vaccine on a regionalized basis in the Americas, with particular emphasis

on Central and South America, is enormous. Questions which must be addressed include availability of expertise for development and production of high quality vaccine, the potential cost savings of producing a serum derived vaccine in an area of moderate disease endemicity (where 2-4% of persons are HBV carriers), potential timetables for vaccine development and production, and possible influences on such programs of less expensive vaccines available from other areas of the world.

d) Vaccination Programs

The other critical aspect of an HBV vaccine policy in the Americas is the design and development of vaccination programs specific to the Region. Because of differing levels of disease endemicity, programs must be developed which take into account the disease epidemiology in each specific locale. One prerequisite for program development will include detailed knowledge of disease epidemiology in the population and in specific "high risk" groups. Another will be considerations of cost of disease prevention not only balanced against program costs but also placed into perspective with other disease priorities in the Region.

Initial strategies for vaccine programs will be derived from both the strategy of high-risk group vaccination used in low endemicity areas, combined with aspects of incipient programs in high endemicity areas--i.e., vaccination of all newborns. Given present costs and moderate disease endemicity in the Region, programs may focus vaccination initially on infants of HBV carrier mothers. However, targeted large-scale vaccination programs for groups in selected hyperendemic areas need to be evaluated within the context of national control programs. For example, in the United States of America, plans for the widespread immunization of specific ethnic groups in Alaska, where the disease is hyperendemic, are already being formulated. Such options need to be evaluated for similar populations in Latin America, such as in the Amazon Basin or in Venezuela.

Table 1

RATES OF REPORTED HEPATITIS IN THE AMERICAS (1977-1980),*
ALL TYPES COMBINED

Country	Rate per 10^5 Avg.	Rate Per year (Range)	Proportion of Cases in Children (% <15 yrs.) (Average)
1. Central America			
Costa Rica	44.8	(24.4- 73.6)	53
El Salvador	47.9	(44.1- 51.6)	-
Guatemala	15.6	(5.3- 22.1)	71
Honduras	42	(32.8- 50.2)	41
Nicaragua	19.4	(7.7- 39)	49
Panama	28	(22.4- 33.9)	66.1
2. Caribbean			
Bahamas	8.8	(6.4- 10)	40.5
Barbados	6	(4 - 8)	10.5
Cuba	170.5	(144.7-190.9)	65.5
Dominican Republic	51.3	(48.6- 54)	-
Grenada	13	(12.2- 13.8)	12
Haiti	1.9	(1.7- 2)	26.5
Jamaica	2.1	(1.7- 2.4)	44
Puerto Rico	16.6	(12.4- 20.3)	-
Trinidad and Tobago	6.8	(3.4- 10.5)	-
3. South America			
Argentina	58.6	(44.3- 67.3)	-
Bolivia	12.4	-	-
Chile	47.7	(37.4- 52.2)	85.3
Colombia	40	(33.9-436)	73
Ecuador	9.4	-	-
Guyana	3.3	(2.4- 4.2)	21.5
Paraguay	9.5	(7.1- 11.3)	50.3
Peru	33.8	(30 - 35.5)	54.3
Uruguay	93.3	(72.9-116.3)	68
Venezuela	23.7	(23.2- 24.1)	-
4. North America			
Canada	9.4		34
Mexico	6.4	(5.7- 7.1)	77
United States	14.5		15

*WHO Statistical Reports (1980-1983)

Table 2

FREQUENCY OF HEPATITIS A, B, AND NON-A, NON-B AS CAUSES OF ACUTE HEPATITIS IN CHILDREN AND ADULTS IN SELECTED COUNTRIES OF THE AMERICAS

Country	Ref.	Children (14 yrs.) Hepatitis Type			Adults Hepatitis Type		
		A	B	NANB	A	B	NANB
Argentina	12,13	85*	4	5	43	35	17
Brazil (II)	14,15	85	5-10	8	27	49	24
Brazil (III)	54	-	16	-	-	54	-
Brazil (IV)+	16	-	-	-	70	25	5
Chile	10,11	78-83	1-2	16-20	71	7	22
Colombia	18	81	-	19	50	25	25
Costa Rica+	17	-	-	-	-	-	12
Honduras	56	-	-	-	-	67	-
Mexico	55	-	13	-	-	-	-
Peru	33	-	-	-	-	42	-
United States	19,20	78	5	16	38	35	27

* % of cases due to agent in group

+ Adults and children

Table 3

PREVALENCE OF HBV IN ADULT BLOOD DONORS

	Country	Ref.	Rate (%) HBsAg (+)	Rate (%) All B Markers	Estimated# HBV Carriers (10^3)
1.	**CENTRAL AMERICA**				
	Costa Rica	24	0.6	20.6	12.7
	El Salvador	§	1.2	-	52.2
	Guatemala	§	2.2 (1.4 - 3)	-	145.6
	Honduras	§	3	-	103.2
	Mexico	24,30	1 (0.33- 1.6)	16.8	669.4
	Nicaragua	§	1.1	-	26.4
	Panama	§	1 (0.7 - 1.4)	-	18.3
				TOTAL 1:	1027.8
2.	**CARIBBEAN**				
	Bahamas	§	1.4	-	3.2
	Barbados	24	1.4	13.1	3.7
	Cuba	§	0.8	-	77.8
	Dominican Republic	24	4.1	82.8	209.9
	Grenada	§	2.1	-	2.0
	Haiti	35,§	2.7 (1.4 - 4)	61	130.4
	Jamaica	§	1.6	-	3.4
	Puerto Rico	24	0.2	11.1	6.7
	Trinidad	37,§	1.4	-	15.8
				TOTAL 2:	452.9
3.	**SOUTH AMERICA**				
	Argentina	24	1.1 (0.7 - 2.1)	18.6	290.3
	Bolivia	34,§	1.6	-	84.6
	Brazil				
	I. South	25	1 (0.2 - 1.8)	-	187.7
	II. Central*	24,25	2 (1.2 - 2.8)	34	1186.2
	III. Northeast+	24	2.5 (1.2 - 3.9)	-	890.5
	IV. Amazonas**	24,26,27	8 (5 -13)	-	411.2
	Chile	24,29	0.5 (0.4 - 0.6)	6.7	54.3
	Colombia	24	1.3 (1 - 1.6)	29.3	333.5
	Ecuador	24	2	35.3	156.2
	Paraguay	§	0.9		26.0
	Peru	24,31-33	1.4 (0.8 - 3.5)	27.3	235.5
	Suriname	24,36	2.3	41	8.6
	Uruguay	§	0.9	-	2.6
	Venezuela	24	2 (1.5 - 2.8)	18	262.4
				TOTAL 3:	4129.6
4.	**NORTH AMERICA**				
	United States	§	0.3 (0.1 - 0.5)	5	654.3
	Canada	§	0.3 (0.1 - 0.5)	5	71.5
				TOTAL 4:	725.8
				TOTAL ESTIMATED:	6336.1

\# Using 1978 est. pop.
* Central - Sao Paulo, S. Santo, M. Gerais, Rio de Janeiro, Mato Grosso, Brasilia
\+ Northeast - Salvador, Bahia, Belem
** Amazonas, Para (excluding Belem)
§ Personal Communication