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REPORT OF INFORMAL CONSULTATION
ON THE PUBLIC HEALTH CONTROL
OF HEPATITIS A

WHO Headquarters, Geneva
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1. INTRODUCTION

Although hepatitis A virus (HAV) infection is self-limited and results in fulminant hepatitis and death in only a small proportion of patients, it is a significant cause of morbidity and attendant economic losses in many parts of the world. The virus is present globally, and rates of infection are inversely associated with levels of sanitation and personal hygiene. Improvements in sanitation and hygiene can reduce the transmission of HAV. However, for countries with lower socioeconomic status, improvement of sanitary conditions results in an increase in the burden of clinical disease, as peak rates of infection shift from early childhood, when infection is largely asymptomatic, to older age groups, when infection is more often symptomatic. Passive immunoprophylaxis using immune globulin (IG) can prevent disease in individuals who are exposed to the virus; however, the protective effect is temporary, and IG is not effective in controlling hepatitis A on a population level. Within the past few years, several vaccines have been developed that provide active immunity and potentially long-lasting protection against hepatitis A. The development of these vaccines represents a major advance in the ability to control HAV infection and reduce the burden of disease.

This document reviews the basic features of the disease and its epidemiology, and considers the measures which are available for the control and prevention of hepatitis A, including use of hepatitis A vaccine.

2. HEPATITIS A

2.1 CLINICAL FEATURES OF HEPATITIS A

The incubation period of hepatitis A, defined as the time period from exposure to the virus to onset of symptoms, averages 28 days, with a range of approximately 15 to 50 days. The severity of acute HAV infection is variable, ranging from an asymptomatic anicteric infection to fulminant hepatitis and death. Early symptoms include fever, malaise, anorexia, nausea, diarrhoea, vomiting and right upper quadrant pain, and usually precede signs of liver injury, including jaundice and dark urine. Liver enzymes, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), rise and generally peak about the time of onset of jaundice. The severity of the clinical illness is highly age dependent; almost all children infected under age 2 do not develop specific signs or symptoms of hepatitis A, while most adults over the age of 18 (greater than 75 %) usually develop characteristic illness with jaundice and dark urine. Infection is self-limited, and the duration of symptoms generally varies from two weeks to two months, although up to 15% of adults have symptoms for as long as 4 months. Mortality from hepatitis A is rare and strongly age-related; fatal infections are more likely to occur in individuals over 40 years of age. Chronic hepatitis with persistence of HAV infection for more than 12 months has not been observed.

2.2 PROPERTIES OF HEPATITIS A VIRUS

Hepatitis A is caused by the hepatitis A virus (HAV), a non-enveloped, positive-stranded RNA virus classified within the genus hepatovirus of the picornavirus family. All human isolates of HAV, while having up to 20-25% variation in nucleic acid sequence,

belong to one serotype. Epidemiologic evidence in humans and studies *in vitro* and *in vivo* support the concept that anti-HAV induced by any isolate of the virus will protect against all viral strains.

While HAV is inactivated by heat above 60-70 C°, it is resistant to drying for at least one month. It can readily survive freezing temperatures, and can persist in fresh or salt water for up to 12 months. The virus may remain infectious for several days or longer in contaminated food. HAV present in fresh or salt water can be concentrated by molluscs, which can be an important source of infection in humans.

2.3 EPIDEMIOLOGY OF HEPATITIS A

In infected persons, HAV replicates in the liver and is excreted in large amounts in the stool. The only known site of replication is the liver. Substantial quantities of infectious virus circulate in the blood for up to 2 to 3 weeks, and virus can also be found in saliva. In persons who develop clinically apparent hepatitis A, excretion of virus in stool at high titres begins two to three weeks prior to onset of illness, and may continue for several weeks in lower titres after jaundice occurs. The level of virus shedding does not correlate with the severity of liver disease. Some patients, especially infants, may intermittently excrete virus for up to six months in stool.

The major route of transmission is faecal-oral. Transmission commonly occurs person-to-person between family members. Person-to-person transmission is also observed among children and staff in day care centres, and among institutionalized persons. Nosocomial outbreaks of hepatitis A with transmission to health care workers have occurred but are rare. As HAV can survive for prolonged periods in the environment, contamination of water and food can result in common source outbreaks. Transmission due to transfusion of blood products does occur, although it is rare.

Worldwide, geographic areas can be characterized by HAV infection patterns of high, intermediate and low endemicity. The level of endemicity correlates with the hygienic and sanitary conditions of each geographic area (*see table 1*).

2.3.1 High endemicity geographic areas

In least developed countries with very poor sanitary and hygienic conditions, which include parts of Africa, Asia, and Central and South America, HAV spreads readily, and most persons are infected as young children. Because most persons in these regions become infected at an age when HAV infection is either asymptomatic or not associated with specific signs or symptoms of hepatitis, reported disease rates in these areas are low and outbreaks of disease are rare.

2.3.2 Intermediate endemicity geographic areas

In developing countries, countries with transitional economies, and some regions of industrialized countries, sanitary conditions are variable, and many children escape infection during early childhood. However, viral circulation remains high, and infection has often occurred by adolescence or early adulthood. Since HAV infection often occurs in these areas in older age groups compared with areas where HAV transmission is more highly endemic, reported rates of clinically evident hepatitis A can be higher. Community-wide

epidemics with extended person-to-person transmission account for a significant amount of disease in these areas. In certain populations, conditions are such that disease trends are cyclical. Virus spreads among children until the population is exhausted of susceptibles. After a period of several years, a new cohort of susceptible children emerges, allowing a return of high rates of viral transmission and clinical disease.

2.3.3 Low endemicity geographic areas

In most industrialized countries, sanitation and hygienic conditions are good, and infection rates in children are generally low. However, community-wide outbreaks continue to occur in some countries, and contribute significantly to the burden of disease. In some countries, day care centres are also important settings for HAV transmission. Common-source epidemics due to contaminated food or water also occur, but contribute less to the overall disease burden. In some countries with very low prevalence (e.g., Northern and Western Europe), the rates of HAV infection are very low in all age groups, and disease tends to occur more commonly among specific risk groups, such as travellers, homosexually active males, and intravenous drug users. Recent investigations of the molecular epidemiology of HAV support these impressions gained from classical epidemiologic studies.

2.4 PREVENTIVE MEASURES AND PROPHYLAXIS

2.4.1 General preventive measures

General measures for hepatitis A prevention include hygienic and sanitary measures used to prevent transmission of any enteric illness. In household settings, good personal hygiene, including good hand washing practices, and attention to proper food preparation are important in reducing the risk of transmission. At the community level, provision of safe drinking water and proper disposal of sanitary waste will reduce the incidence of hepatitis A. Good hand washing practices and personal hygiene among food handlers, as well as good food handling techniques, are important in preventing food-borne outbreaks of hepatitis A. Prevention of hepatitis A outbreaks associated with uncooked shellfish relies upon surveillance of water beds where shellfish are harvested to ensure that there is no evidence of faecal contamination, and control of the commercial distribution of shellfish from unsupervised areas.

2.4.2 Immune globulin

IG is a preparation of antibodies made from pooled human plasma using the Cohn-Oncley cold ethanol fractionation procedure or other techniques, and is administered intramuscularly to prevent hepatitis A. If given before exposure or within two weeks after exposure to the virus, IG is more than 85% effective in preventing symptomatic hepatitis A. Protection is conferred by passive transfer of anti-HAV. In Japan and certain European countries, as the hepatitis A incidence (and consequently the anti-HAV prevalence among plasma donors) has decreased over time, titres of anti-HAV in IG have also declined. In some European countries, specific high titre anti-HAV IG is available for prevention of hepatitis A. IG for intramuscular use made under good manufacturing practices with the Cohn-Oncley procedure has never been shown to transmit hepatitis B virus (HBV), hepatitis C virus, HIV, or other blood-borne agents.

2.4.3 Hepatitis A vaccines

The isolation and propagation of HAV in cell culture were critical steps necessary for the successful development of hepatitis A vaccines. Several HAV isolates have been propagated in tissue culture and have been used to make both inactivated and attenuated vaccines. The use of any hepatitis A vaccine should be subject to approval by the appropriate national control authorities.

(a) Live attenuated hepatitis A vaccines

Several live attenuated hepatitis A vaccines are currently under development and two are now licensed in China. Some investigators believe that attenuated vaccines may have substantial advantages over inactivated vaccines in that they may require smaller quantities of virus and only a single dose of vaccine, resulting in much lower costs, and possibly a longer duration of immunity. For these reasons, development of these vaccines should be encouraged. However, several aspects of attenuated vaccines must be assessed in greater detail including possible reversion to wild type, the significance of transient and mild elevations of liver enzymes after administration, and possible transmission of vaccine virus to contacts, additional controlled trials are needed with attenuated vaccines to better assess both safety and efficacy.

(b) Inactivated hepatitis A vaccines

Inactivated hepatitis A vaccines are generally prepared by purification of virus propagated in cell culture, followed by formalin inactivation and possibly adjuvanting with aluminum hydroxide. Similar methods of propagation, inactivation and adjuvanting are used to prepare inactivated poliovirus vaccines. No serious adverse reactions have occurred in phase II and phase III clinical trials with several of these vaccines. As the virus in the vaccine is inactivated, immunodeficiency or HIV infection do not contraindicate its administration. Immunogenicity studies have shown that 70-90% of persons develop anti-HAV following a single dose, and nearly 100% of persons have anti-HAV following two doses of vaccines prepared by several different manufacturers. Antibody levels obtained after a single dose of vaccine are often higher than those obtained after a single dose of IG, and substantial levels of anti-HAV neutralizing antibody are present in the majority of recipients of a complete immunization series. One immunogenicity study has suggested that simultaneous administration of large doses of IG with the first vaccine dose may lower the active antibody response. However, the diminution in antibody titre does not appear great enough to expect an impact on the protective effect of the vaccine.

Animal challenge studies have shown that inactivated hepatitis A vaccines may confer protection against disease. Recent field efficacy trials in children with two separate HAV vaccines produced from different strains have demonstrated 94%-100% efficacy in preventing clinical hepatitis A. The duration of protection after vaccination is unknown. However, antibody decay studies suggest that measurable antibody will persist for many years. Continued observation of immunized groups will be required to determine the need for additional late booster doses of vaccine. An inactivated hepatitis A vaccine is now commercially available in several European countries and several different vaccines are expected to be widely available in the near future.

(c) **Use of the inactivated hepatitis A vaccine**

i. **Route and schedule**

The recommended route and schedule for administration of inactivated hepatitis A vaccines may vary according to manufacturers and national control authorities. However, these vaccines are likely to require two or three doses for long lasting protection.

ii. **Prevaccination testing for susceptibility and postvaccination testing for serologic response**

HAV infection induces lifelong immunity, therefore persons who have anti-HAV from prior infection do not need to be vaccinated with hepatitis A vaccine but do not react adversely to immunization. Screening for anti-HAV prior to vaccination may or may not be cost-effective depending upon several factors, including the expected prevalence of anti-HAV in the population, the cost of the screening test, and the cost of the vaccine. For example, anti-HAV prevalence is generally greater than 50% among persons born in developing countries and persons born in industrialized countries prior to 1945. Prior testing in these persons may be cost effective. Anti-HAV prevalence among persons born in industrialized countries after 1945 is generally lower than 25%. Therefore, vaccination without prescreening is usually cost-effective in these persons.

Due to the high immunogenicity observed with inactivated hepatitis A vaccines, postvaccination testing for serologic response is not generally indicated.

2.5 RECOMMENDATIONS FOR USE OF IMMUNE GLOBULIN AND HEPATITIS A VACCINE IN SPECIFIC GEOGRAPHIC AREAS

Appropriate public health use of hepatitis A vaccine requires up-to-date epidemiological information. Surveillance of acute hepatitis, with differentiation of hepatitis A and B as a minimum, is an essential element of this epidemiological picture and should be a target for countries in which it does not currently exist.

2.5.1 High endemicity geographic areas

In these parts of the world, the vast majority of persons become infected prior to 5 years of age without evidence of hepatitis, and develop lifelong immunity. However, occasional mortality from fulminant hepatitis A does occur. While most clinical cases of hepatitis A are seen in children, adults who escape childhood infection remain susceptible to infection and a more serious clinical hepatitis in late life. With socio-economic development, infection will shift to older ages thus increasing the disease load in adults. Despite the high prevalence of antibody in the population, the virus perpetuates in the region due to its high physical stability.

In such highly endemic areas, it is difficult and impractical to identify risk groups for transmission of hepatitis A and any interventional strategy must take into account that children below 5 years are the single most important risk group for infection in this setting. However, taking into consideration the relatively small disease burden from hepatitis A, the present expense of the vaccine, and the uncertain duration of immunity from HAV vaccination, the cost-benefit of an infant mass immunization programme may be too low

for most developing countries in the light of other pressing health problems. As vaccine costs decrease, and more data become available concerning duration of immunity, these cost-benefit considerations should be reassessed. The increasing age of infection with resulting increased hepatitis disease burden should also lead to a reassessment of the cost-benefit of a mass immunization programme, and developing countries, where this is already the case, may wish to formulate a programme at an earlier stage.

It should also be noted that socio-economic development in these areas is usually an uneven process so that improvement in parameters affecting the risk of hepatitis A infection in some households may outpace that of the community as a whole. As a result, individuals in such households are less likely to be exposed to HAV at an early age. However, as susceptible adults, they become exposed to infection when they interact with the environment outside their own homes. In such individuals, hepatitis A vaccination may be considered in school, before employment, or attendance in institutions of higher education.

It is strongly emphasized that efforts to improve water supplies and sanitation levels should continue to have a high priority in reducing infection rate with hepatitis A.

2.5.2 Intermediate endemicity geographic areas

HAV infection occurs in high rates in older children and adults and can result in significant morbidity. In these areas hepatitis A occurs endemically and in large community-wide epidemics. In considering the potential use of vaccine, each country must determine the relative public health importance of hepatitis A vaccination based upon the disease burden, other health priorities and available resources. A variety of strategies of hepatitis vaccination in these areas could be formulated depending on the specific disease situation. Ideally, when vaccine cost and availability permit, the ultimate aim should be large-scale (mass) vaccination. Initially, however, priority groups should be defined based on the local situation. For example, public health authorities may select institutionalized, pre-school children, municipal workers and/or army recruits for priority immunization.

(a) Community-wide epidemics

Community-wide epidemics of hepatitis A contribute to a substantial amount of the hepatitis A burden in intermediate and low endemicity areas. These outbreaks are often large, with highest rates in children and young adults, and in households which are larger in size and with lower socioeconomic status. IG has been ineffective in sustained control of HAV transmission in affected communities. Hepatitis A vaccine should be strongly considered for this purpose. Vaccination strategies may vary from community to community. Further studies are required to define the optimal immunization strategies.

2.5.3 Low endemicity geographic areas

In industrialized countries, most children escape HAV infection, and viral circulation is low in the general population. However, hepatitis A continues to occur within certain groups such as travellers, homosexually active men, and illicit drug users. Day care centres, and communities with lower socioeconomic level are important settings for the transmission of HAV. If administered to travellers, IG is highly effective in preventing hepatitis A for travel related exposure of less than 3 months; for longer periods, repeated injections are necessary. Studies have also shown that appropriate administration of IG in day care

centres where cases of hepatitis A are identified can control outbreaks and prevent further transmission. Administration of IG generally has not been effective in preventing community-wide outbreaks of hepatitis A since continued circulation of virus outlasts the duration of IG protection.

Hepatitis A vaccine, by affording protection of longer duration than IG, may offer great advantages in preventing and controlling hepatitis A in these groups and settings. If the vaccine is shown to be protective when administered after exposure to HAV, then prevention strategies using hepatitis A vaccine instead of IG can be considered in the post-exposure setting. Studies addressing whether the vaccine protects when first administered after exposure are needed. While the vaccine has been shown to be efficacious in controlled trials, data are needed on the comparative programme effectiveness of using hepatitis A vaccine instead of IG to prevent disease in a community-wide setting. Economic analyses are needed to evaluate whether vaccination in these groups and settings should be considered. Until data are available, few definite recommendations can be made. Some of the possible uses of hepatitis A vaccine are discussed below:

(a) Travellers

Persons from low endemicity geographic areas who travel to areas of intermediate or high endemicity are at risk for acquiring hepatitis A. In general, travellers to the United States, Canada, Western Europe, Japan, Australia and New Zealand do not have a significantly increased risk of hepatitis A and, therefore, IG prophylaxis or vaccination is not warranted. Travellers to other areas should receive hepatitis A vaccine prior to their departure, especially for travel of long duration, and for those who travel repeatedly. The issue of prescreening of travellers for anti-HAV prior to vaccination has been discussed above.

(b) Day care centre children and staff

Outbreaks have been recognized among children attending and employees working at day care centres, and in some instances these outbreaks may be the source of larger community epidemics. Outbreaks have been predominantly recognized in centres with children who are not toilet-trained, where clinical disease occurs in staff, parents and older siblings of day care centre attendees. The use of IG has been well documented to control outbreaks of disease in these settings. Although this has not yet been studied, presently available data from hepatitis A vaccine efficacy studies suggest that vaccine may be able to replace IG in control of day care centre outbreaks. Studies should be done to evaluate the effectiveness of vaccine in controlling recognized outbreaks and preventing further transmission. Vaccines have the additional benefit of providing long-lasting protection. The cost-effectiveness of pre-exposure vaccine administration to staff and children in day care centres should be evaluated.

(c) Persons in residential institutions

Historically, hepatitis A outbreaks in institutions for the developmentally disabled are frequent. As conditions within institutions have improved over the past decades, the incidence and prevalence of the disease have decreased, although large outbreaks can occur if the virus is introduced. Outbreaks in these institutions may be controlled with IG. As with day care centres, the role of vaccine in replacing or supplementing IG in controlling or preventing outbreaks needs to be studied. These considerations also apply to the

potential use of vaccine to control and prevent outbreaks in other residential institutions, such as prisons.

(d) Homosexually active men

Extensive outbreaks among homosexual men have been recognized in urban areas in the United States, England and Australia. Thus, homosexually active men should be considered for vaccination with hepatitis A vaccine.

(e) Users of illicit injectable drugs

Within the past decade, hepatitis A outbreaks have been reported with increasing frequency among injecting drug users, both in the United States and in Europe. As these individuals may have underlying liver disease due to chronic infection with other hepatotropic viruses, they may be at higher risk for severe complications from hepatitis A. Consideration should be given to vaccination of these drug users.

(f) Food handlers

Food handlers, if infected with HAV, can be the source of food-borne epidemics. When a food handler is recognized with HAV infection, and especially when outbreaks are recognized, it is often too late to provide prophylaxis to patrons of the food establishment. However, in this circumstance IG is recommended in some countries for other food handlers at the establishment. If it is determined that vaccine provides post-exposure protection, consideration should be given to use of vaccine in this situation. Economic analyses are needed to determine whether pre-exposure vaccination of food handlers is indicated.

(g) Community-wide epidemics

This is discussed above in section 2.5.2.

(h) Health care workers

Nosocomial outbreaks from infected patients to health-care workers are rare. There is no convincing epidemiologic evidence that health care workers in general are at increased risk for hepatitis A. Thus, additional studies are required to determine whether routine hepatitis A vaccination of health care workers is indicated.

(i) Persons with chronic liver disease

Since clinical hepatitis A may be more severe in persons with chronic liver disease due to hepatitis viruses or other etiologies, use of inactivated hepatitis A vaccine in these persons should be considered.

(j) Other groups

Data regarding risk to sewage treatment plant workers are limited, and no outbreaks have been observed among this group. Although, at this time available data are insufficient to recommend routine vaccination of sewage treatment plant workers, further studies to more accurately quantitate the risk are needed.

2.6 FUTURE CONSIDERATIONS

The epidemiologic characteristics of hepatitis A strongly suggest that effective control of hepatitis A in populations with high and intermediate levels of endemicity could only be achieved by universal immunization. As groups at high risk for hepatitis A in low endemicity areas may be difficult to access with vaccine programmes, universal immunization may be required in these areas as well. The high cost of inactivated HAV vaccines is the major factor restricting the ability of such vaccines to reduce disease burden. As attenuated HAV vaccine, or potentially recombinant, live-vectored hepatitis A vaccines may offer substantial advantages in terms of the costs, production and administration, their development should be strongly encouraged.

Several important questions remain regarding inactivated hepatitis A vaccine, including whether such vaccines may provide protection when given shortly after exposure, and the relative merits of IG and vaccine in this setting; the duration of protection and the extent of immunologic memory provided by the vaccine in pre-exposure immunization; the effect of simultaneous administration of IG and vaccine on immunogenicity; and the cost effectiveness of various strategies of hepatitis A vaccine use. Studies addressing these questions should be encouraged, and when results are available in the future, they will greatly influence the decisions on how the hepatitis A vaccine can be used to prevent and control HAV infection.

The development of vaccines combining inactivated hepatitis A vaccine with other vaccine antigens in a single formulation would have significant advantages due to the need for fewer injections, lower cost, simplicity of administration and greater acceptance by parents and physicians. Research in combining hepatitis A vaccine with other vaccines (hepatitis B or DPT) should therefore be encouraged.

2.7 CONCLUSION

Hepatitis A virus infection is a significant cause of morbidity in many parts of the world, and hepatitis A vaccines will be important tools for prevention and control of HAV infection. The use of this vaccine should be adapted to specific epidemiologic circumstances existing within a geographic region, with special attention to the cost effectiveness of immunization programmes.

TABLE 1

EPIDEMIOLOGIC FEATURES OF HEPATITIS A
VIRUS INFECTION WORLDWIDE

HAV endemicity	Usual age of infection	Risk groups for clinical disease	Outbreaks
High	< 5		rare
Intermediate	5 - 15	many	common: community wide, foodborne, waterborne, shellfish
Low	> 20	travellers, drug users, homosexually active men	occasional: day care, foodborne, waterborne, shellfish, community wide