Immunization Dialogue

Hepatitis A Vaccine

Hepatitis A vaccine has been recently introduced in the international market. It is likely that in the near future, this product may also be launched in India. We need several clarifications including the need for routine hepatitis A immunization and its efficacy and safety. In this context, Dr. T. Jacob John, Professor and Head, Department of Microbiology and Virology, Christian Medical College Hospital, Vellore, Tamil Nadu 632 *004 answers important questions posed by us. Professor Jacob John, a leading International Vaccinologist is the current Chairman of the IAP Committee on Immunization.*

-Editor-in-Chief

Q 1. *Hepatitis A is a more common infection than hepatitis B in pediatric practice in our country and is also known to occur in an epidemic form. However, the stress is on hepatitis B immunization instead of hepatitis A immunization. What are the reasons for this ?*

A 1. Hepatitis A virus (HAV) is transmitted by the feco-oral route, very much like polioviruses. In India and many developing countries HAV infection is so common that all children have antibodies to it by about 10 years of age. When HAV infects children below 10, about 90% infections are either subclinical or too mild to be noticed; only some 10% result in acute hepatitis with jaundice. Moreover, mortality is extremely rare in hepatitis A. There is no chronic infection or chronic liver disease due to HAV. For these reasons there is very little public health importance for hepatitis A in India at the present time.

On the other hand, in countries with better hygiene, the spread of the virus is much slower and infection is spread over a wide range of age groups. Primary infection in adults results in acute hepatitis with jaundice in over 80% of subjects. Mortality is also higher, since a small proportion of infected adults develop fulminant hepatitis. For these reasons, the priority for prevention by immunization is 'higher in countries with less HAV infection than in countries like India with widespread HAV infection.

The issues concerned with the need for prevention of hepatitis B virus (HBV) infection have already been discussed earlier. Briefly, what we want is the prevention of chronic HBV infection with it's attendant risks of cirrhosis of liver and chronic active hepatitis; of acute fulminant hepatitis; of nosocomial HBV infection in patients and staff; of vertical transmission of HBV; and most important, the prevention of the perpetuation of the large reservoir of HBV infection in our population.

Q 2. *What are the various types of hepatitis A vaccines available?*

A 2. There are two types of HAV vaccines in current use in different parts of the world, namely killed virus vaccine and live virus vaccine. Vaccine develop-

merit was made possible when HAV was adapted to replicate in cell cultures. Subsequent attempts to develop an oral or injectable live virus vaccine resulted in over-attenuation of the virus and poor rates of 'take' and immunogenicity. Chinese scientists succeeded in developing an injectable live virus vaccine, which is in current use in China. Although 1 do not have authoritative information, it is my understanding that a single-dose live HAV vaccine is now in routine use in childhood immunization in China.

The killed virus vaccine is .prepared by formaldehyde-inactivation of HAV. It has been found to be safe and effective in phase 1, 2 and 3 trials. Many European countries have licensed this vaccine (Havrix, Smithkline Beecham Biolo-gicals) in 1993, for use in adults or children. The vaccine is highly immunogen-ic; even a single dose induces serocon-version in over 90% of subjects. Two doses given 1 mo (or 4 wks) apart, as recommended by the manufacturers, induce seroconversion in 98% or more subjects. Protective vaccine efficacy is also equally high. In the United States another killed HAV vaccine has been developed by Merck Sharp & Dohme.

Q 3. *Is hepatitis A vaccine likely to be available for clinical use soon in India ?*

***A* 3.** Regarding the likelihood of the availability of HAV vaccine in India, we must consider how newer vaccines have become available in the past. If the manufacturers or their agents wish to market their vaccine, an application is made to the Drugs Controller, Ministry of Health. Once a licence is issued, the vaccine could be marketted in India. The HAV vaccine is quite expensive (US $25 per dose) and the market in India is not very clear; for these reasons, presumably, the vaccine has not yet been licensed in India, to the best of my knowledge. An alternative channel is for the Ministry of Health to introduce a new vaccine into the National Immunization Programme (NIP). However, in the past only already licenced vaccines had been included in NIP. For example, measles vaccine which was introduced in NIP in 1985 had been licensed in the country over a decade earlier.

My personal plea has been, for over 20 years now, for the establishment of an Immunization Policy Recommending Body with representation from Ministry of Health, Indian Council of Medical Research. Indian Academy of Pediatrics, and other relevant agencies if any. As far as HAV vaccine is concerned the priority is low in India. But there should be a mechanism to look not only at HAV but also many other newer vaccines.

Q 4. *What is the reported efficacy and safety of hepatitis A vaccine ?*

A 4. A large scale efficacy trial of the European HAV vaccine was conducted in school-age children in Thailand. The schedule consisted of 2 doses 1 month apart and a booster after about 10-12 months. The protective efficacy was more than 95% after the 2 doses and virtually complete after 3 doses. The safety record of the killed HAV vaccine also has been excellent, ft is an aluminium hydroxide adjuvanted vaccine; hence pain and tenderness at the site of injection in some vaccines do occur.

Q 5. *Should hepatitis A vaccination be recommended in India ?*

A 5. In my personal, considered,

opinion HAV vaccine need not, (and should not) be recommended for children or adults in India at the present time.

Q 6. *What is the duration of protection after hepatitis A immunization ?*

***A* 6.** It is too early to discuss the duration of protection of HAV vaccine since it was licensed for general use in some countries as recently as in 1993. However, based on available information of the nature of antibody response, after 2-dose primary and one booster doses, the protection may be long-lasting *i.e.,* many years. We will have to wait for more data on this subject.

Q 7. *What is the recommended route, site, dose, age and schedule for hepatitis A vaccine ?*

A7. It is perhaps premature to define the details addressed in the question. However, the manufacturers do make their guidelines clear in the leaflet. As an aluminium salt adjuvanted vaccine, it is meant to be given IM, the preferred site being the deltoid muscle. However, if it is given SC, it would not matter too much in terms of reactogenicity or immunogenicity. Occasionally adjuvanted vaccines given by the SC route may give rise to nodule formation.

The vaccine comes with the dosage clearly defined *(e.g.,* 0.5 ml). The potency of the SKB vaccine is measure in ELISA units (EU). The vaccine contains 750-1000 EU. The potency of the MSD vaccine is measured in terms of the nanogram content of viral protein. One dose is made of about 400 ng.

The killed HAV vaccine may be given at any age. Two doses one month apart is the primary course. Even the first dose alone is somewhat protective and many travelers from developed countries do take at least one dose, or 2 doses before travel. A booster is recommended about one year later.

Q 8. *What are the side effects and contraindications for hepatitis A vaccine ?*

***A* 8.** As mentioned earlier, based on the available but relatively limited data we can say that the side effects of HAV vaccine are mild and infrequent. Mild tenderness and pain at the site of injection occur in upto 50% of vaccines after the first dose. With the second dose the reaction seems to be less frequent. Rarely a vaccine develops low grade fever, lasting about one day; this happens is some 2-4% of subjects. There are no clear contraindications that have been defined. Those who are already immune do not require the vaccine. Its safety in pregnancy can be assumed, but should be proven by studies. Allergic reaction to the first dose is a warning for caution with subsequent doses.

Q 9. *What are the recommended storage conditions for hepatitis A vaccine ?*

A 9. Like all other killed vaccines in liquid presentation, HAV vaccine also is to be stored at +4 to +8°C. Again, like all vaccines adjuvanted with aluminium salts, it should not be frozen.

Q 10. *Can hepatitis A vaccine be administered simultaneously with other vaccines and immunoglobulin ?*

***A* 10.** There appears to be no reason why HAV vaccine may not be given simultaneously with other vaccines. Large doses of normal human immunoglobulin administered at the time of HAV immunization reduces the immunogenicity of the vaccine.